LEAD POISONING – AN OVERVIEW

Subash Vijayakumar¹, M. Sasikala¹, R. Ramesh²

¹Associate Professor & Head, Department of Pharmacy practice, Vaagdevi College of Pharmacy, MGM Hospital, Warangal, A.P, India.
²Assistant Professor Department of Pharmaceutics, Aurobindo College of Pharmaceutical Sciences, Warangal, India.

ABSTRACT

Lead is a natural component of the earth’s crust with trace amounts existing in soil, water and plants. The aim of this study was to review the clinical features, kinetics, diagnosis & management of the poison. We develop a search strategy to find any publication about lead and its management. So we search Science Directory, Bentham Publishers, Google Search, Dove press & Pubmed bibliography database using the key phrase diagnosis, clinical features and its treatment. Our review enlighten the treatment allow a better prognosis with lower mortality rates. This review resulted, on the basis of relevant literature its suggested that future strategies have to be developed for innovation of newer molecules for treating lead poison & minimizing the complications associated with lead toxicity. This review may provide clear information to health care providers to pay more attention to develop a new drug molecule to manage the lead poison.

Keywords: Children, Lead, Battery, Household, Paint, Tissue and Bone.

INTRODUCTION

Lead is the commonest metal involved in chronic poisoning. Lead is a natural component of the earth's crust with trace amounts existing in soil, water and plants. Lead is practically immobile but becomes highly toxic when mined and used by people. Environmental sources of lead may be from air, food and water pollution. Leaded gasoline and paints were thought to be the main sources of lead pollution in the environment. A Greek physician described the symptoms of lead poisoning in the second century B.C. Later, other physicians described the clinical manifestations of lead poisoning, but many failed to make a connection between the symptoms and the causative agent. Observations that workers in the lead trade had problems with sterility, abortion, stillbirth, and premature delivery prompted a British Royal Commission in 1910 to recommend that women be excluded from the lead trades. Lead poisoning in children was first described in 1892 in Australia by Gibson, an ophthalmologist, who had identified the source of lead and its probable route of entry in to children [1]. It is well known that lead (Pb), as a kind of heavy metals, is a dangerous and important environmental pollutant. Lead has been used for thousands of years and its poisoning effects have been recognized for several centuries. Lead can cause pathophysiological changes in several organ systems including central nervous, renal, hematopoietic, and immune system. Among these damages, a very important issue is that lead can strongly affect intelligence development of children. Many studies indicated that neuro development and cognitive development of children were adversely affected by low level lead exposure [2]. In 1991 the U.S. Centers for Disease Control and Prevention (CDC) established a blood lead intervention level or acceptable blood lead level (BLL) of 10 mg/dL for children (CDC, 1991) along with specific intervention recommendations (Table1) years have passed since a parallel and failed commitment to prevent childhood lead exposure. This commitment was preceded

Corresponding Author:- Subash Vijayakumar Email:- vijayvijay66@yahoo.co.in
by a gradual lowering of what was considered to be an acceptable BLL in children, starting in 1960 with a CDC value of 60 mg/dL. This gradual reduction in what was considered a “safe” or “acceptable” blood lead level tracked the evidence from research in both laboratory animals and humans that even lower levels of lead exposure induced harmful consequences. During the last 15 years, this trend has continued. Numerous studies have repeatedly demonstrated adverse neuro developmental effects, such as lowered IQ, at BLLs below 10 mg /dL [3].

Physical appearance
Elemental lead exists as highly lustrous, heavy, slivery grey metal with a cubic crystal structure that assumes a bluish tint as it tarnishes in air. It is quite soft and malleable. Several of its salts occur as variously coloured powders or liquids and are used widely in industry and at home producing cumulative toxicity on chronic exposure [4].

History
Lead’s low melting point and malleability made it one of the first metals smelted and used by human society. Roman society found many uses for lead, including pipes, cooking utensils, and ceramic glazes, and a common practice was to use sapa, a grape syrup simmered down in lead vessels, as a sweetener and preservative. Postindustrial lead use increased dramatically and today, lead is the most widely used non-ferrous metal, with global production on the order of 9 million tons annually. The US annual production of lead averages 1.1 million tons, of which about 0.5 million tons are newly mined and 0.6 million tons are recycled from scrap metal. Lead is used widely in industry for its water proofing and electrical and radiation-shielding properties. Both metallic lead (as grids) and lead oxide (in paste) are used in electric storage batteries and these account for almost two-thirds of annual US use. Because batteries last only 27 months on average, and about 80% of battery lead is resmelting as scrap, this single product accounts for the largest source for raw lead the secondary smelting and refining industry. Lead alloys are used to shield power and telephone cables, in the printing industry to produce type, and in solders. Solder is used in many industries, including tin can production, plumbing and repair operations and the automobile industry, particularly radiator production and repair. Sheet lead lines chemical reaction containers and is used in medical and industrial radiation shields. Metallic lead is also used for ammunition manufacturing bronze and brass production and for annealing, galvanizing and plating. Inorganic lead compounds have historically been considered among the highest-quality paints. Lead compounds are used as stabilizers in the production of polyvinylchloride plastics, in glazes for ceramic ware, and in the manufacture of glass intended for crystal optical and electronic applications, such as color television pictures tubes, lead azide and styphnate are used in explosives. Lead salts, particularly lead acetate (sugar of lead), were used medicinally in the early 19th century for control of bleeding and diarrhoea; recent examinations of hair samples from Andrew Jackson identified elevated lead levels, compatible with his described chronic affliction of “bilious colic” a syndrome including constipation and severe, cramping abdominal pain [5].

Epidemiology
Lead poisoning affects persons of all ages, but tends to cluster into several distinct at risk populations. The scope and clinical significance of the problem are most severe in young children, aged 1-6 years, whose primary source of exposure is deteriorated lead paint in their home. The developed countries declared such childhood lead poisoning “the most important environmental health problem for young children. The second large, affected group is adults, exposed at their place of work, whose occupation involves lead smelting or reclamation, construction or demolition, or the manufacture or repair of lead containing materials. General environmental exposures from contaminated air, water and food are uncommon in advanced societies today, but may still affect an entire community under special circumstances. Exotic sources are also reported sporadically including exposures to contaminated folk medications, cosmetics, ingested lead foreign bodies, retained bullets, artists or other hoppy materials, firing ranges illicit distilled alcoholic beverages, and substances of abuse [7].

Uses
It is used in cosmetics, Internal and topical medicinal preparations, paint pigments, and glazes since early in recorded history. Among cosmetics lead tetraoxide is the most common compound “sindoor” applied by married hindu women to the parting of their scalp hair, while lead sulphide is used as an eyeliner by muslim [4].

Usual fatal dose
This is not really relevant to lead since acute poisoning is very rare. The average lethal dose is said to be 10 g/ 70 kg for most lead salts. While it is 100mg tetra ethyl leads [4].

Lead adversely affects all body systems and inhibits enzymes required by all cells. Lead modifies the function and structure of the kidney, bone, the central nervous system, and the hematopoietic system. It also produces adverse biochemical, histopathological, neuropsychological, teratogenic and reproductive effects. Similarly to other toxins, the behavioural manifestations of lead poisoning are dose-dependent. Lead at blood lead levels 70 mg /dl is life-threatening and can
cause encephalopathy in children. Such poisoning has symptoms that may initially include lethargy, abdominal cramps, anorexia, and irritability and can progress to vomiting, clumsiness, ataxia, alternating periods of hyper irritability and stupor, and then finally coma and seizures. The sequelae include neurological signs and mental retardation. However, due to the prohibition of the use of leaded paint in 1978 and the elimination of leaded gasoline in 1985, average blood lead levels in the United States have decreased and children with blood lead levels 70 mg/dl are relatively rare. Since children with potentially lethal blood lead levels are now in frequently encountered, the poisoned patient who comes to the attention of clinicians presents with entirely different symptoms. Patients with lower levels of exposure may complain of stomach pains and loss of appetite and could have anemia. These symptoms “y” are not present in all poisoned children, or even the majority, and in any case, do not unequivocally point to lead as the culprit’’ (Lidsky and Schneider, 2003). Low lead levels may still be neurotoxic and numerous investigations have documented that these patients’ symptoms are in the realm of neurobehavioral functioning [9].

The federal Occupational Safety and Health Act (OSHA) were passed. This led, in 1971, to the adoption of an interim Permissible Exposure Level (PEL) of 200 µg/ml for lead dust in air. In 1979, a permanent OSHA standard was implemented. It specified a PEL of 40 µg/ml, as well as a blood lead concentration limit of 50 µg/dl. The Centers for Disease Control defines an elevated BLL as 10 Ag/dL. This advisory level has been continually reduced over the past few decades, from 60 Ag/dL (1960–1970), to 30 Ag/dL (1970–1985), to 25 Ag/dL (1985–1991), to 10 Ag/dL (1991). As new studies have demonstrated, adverse health effects occur at BLLs below 10 Ag/dL. No threshold for harmful effects of post natal lead exposure has been identified. Low-leaded gasoline (0.15g/L) was available in four metropolitan cities (Bombay, Calcutta, Chennai and Delhi) in December 1994, in state capitals in September 1995, and in the entire country in December 1996 [10].

Clinical features
a) The hematopoietic system (microcytic anemia from an abnormal and impaired production and an increased destruction of red cells).
(b) The nervous system (encephalopathy, mainly in children, peripheral neuropathy, mainly in adults).
(c) The kidney (tubular damage in acute intoxication, interstitial-glomerular fibrosis and tubular atrophy in chronic intoxication).
(d) The gastro-intestinal tract (colic, constipation and diarrhea).
(e) Various effects on bone, liver, defense mechanisms of the body, hormonal secretion etc.
(f) Organic lead.

ACUTE POISONING
This is rare. Many reported cases of acute poisoning may actually be exacerbations of chronic lead poisoning when significant quantities of lead are suddenly released into the blood stream from bone. Symptoms include metallic taste, abdominal pain, constipation or diarrhoea (stools may be blackish due to lead sulphide), vomiting, hyperactivity or lethargy, ataxia, behavioural changes, convulsions, and coma.

CHRONIC POISONING (plumbism or saturnism)
Children show weight loss, weakness, and anaemia. The first signs in children may be subtle neurobehavioural deficits adversely affecting classroom behaviour and social interaction. Adults manifest vague gastrointestinal and CNS complaints; wristdrop and colic rarely occur.
A. Mild Toxicity (BL 40 to 60 mcg/100 mL)
  ➢ Myalgia
  ➢ Paraesthesia
  ➢ Fatigue
  ➢ Irritability
  ➢ Abdominal discomfort
B. Moderate Toxicity (BL 60 to 100 mcg/100 mL)
  ➢ Arthralgia (especially nocturnal)
  ➢ Muscular exhaustion
  ➢ Tremor
  ➢ Headache
  ➢ Diffuse abdominal pain
  ➢ Anorexia, metallic taste, vomiting
  ➢ Constipation
  ➢ Weightloss
  ➢ Hypertension
C. Severe toxicity (BL more than 100 mcg/100 mL)
  ➢ Lead palsy - Wrist or foot drop
  ➢ A bluish black lead line on gums (Barton’s line) cramps. There may be tenderness around the umbilicus
  ➢ Lead colic- intermittent severe abdominal cramps.
  There may be tenderness around the umbilicus
  ➢ Lead encephalopathy – It is more common in children and is often associated with organic lead toxicity, especially tetraethyl lead or TEL which is lipid soluble and is distributed widely in lipophilic tissues such as the brain. TEL is metabolised to triethyl lead which is the major toxic compound. There is sudden onset of vomiting, irritability, headache, ataxia, vertigo, convulsions, psychotic manifestations, coma and death. Mortality rate is around 25%. Even if recovery occurs, there is often permanent brain damage manifesting as mental
retardation, cerebral palsy, optic neuropathy, hyperkinesis and periodic convulsions.

Facial pallor, especially circumoral is said to be a characteristic feature of chronic lead poisoning and is due to vasoparn, though anaemia may contribute to a significant extent. The anaemia that is encountered in plumbism is similar to that due to iron deficiency, i.e., it is hypochromic and microcytic in type; but anaemia due to the latter is neither associated with reticulocytosis, nor is basophilic stippled cells seen. There are some reports suggesting that while early in the course of poisoning (particularly in children), lead induced anaemia is microcytic and hypochromic, in the chronic stage, it often changes to normochromic, and normocytic. Anaemia is not a prominent feature in organic lead poisoning. Basophilic stippled cells are also not commonly encountered.

Increasing blood levels in children have been correlated with hearing impairment, developmental delay, aggressive, hypertensive and antisocial behaviour, visual problems and growth retardation. Lead is transferred across the placenta. It can affect reproduction in males and females, and affects neurodevelopmental milestones in children with both prenatal and postnatal exposure. Lead may decrease gestation time at maternal blood levels lower than 25mcg/100mL. At maternal blood levels greater than 15mcg/100mL, there may be a modest risk for intrauterine growth retardation. Lead poisoning during pregnancy has been associated with prematurity, low birth weight, and impaired growth. Lead is increasingly being implicated as a carcinogen. Social lead salts have produced tumours in experimental animal studies [4].

FETAL EXPOSURE TO LEAD

Multiple studies have established the fact that lead crosses the placenta of pregnant women and enters the fetal tissues with lead levels in the mother’s blood comparable to concentrations of lead in umbilical cord blood at birth [11]. Correlation coefficients between lead in umbilical cord blood and blood lead in the mother have been reported as high as 0.84 [12]. The fact that the blood-brain barrier in the newborn is relatively immature raises additional concern as to the presence of lead in fetal tissues. The central nervous system does most of its growing during fetal life and during the year.

METABOLISM AND BIOCHEMISTRY

Differences between children and adults in several aspects of lead metabolism contribute to the greater susceptibility of children to lead toxicity. These include intestinal absorption, bone metabolism, and the rapid development of the nervous system in young children. Absorption of ingested lead from water, food, or dust is the major source of lead in non-occupationally exposed individuals. Lead absorption is approximately fivefold greater in children than in adults and is increased by fasting, iron deficiency, and low dietary calcium [13]. Following absorption lead is distributed to two main compartments. The readily exchangeable compartment comprises blood and soft tissues (liver, kidney, brain) in which levels are independent of age. Over 95% of blood lead is contained within erythrocytes and blood – lead levels represent relatively short-term exposure [14]. In the adult, almost 90% of the total body lead burden is contained in bone, within a slowly exchangeable pool that includes mitochondrial lead. Accumulation of lead in bone begins in fetal life and continues into old age. The half-life of lead in adult bone has been estimated in different models to be 10-20 years, but in rapidly growing children with active bone turnover, it may be much less [15]. The bone lead reservoir is important in situations of increased bone turnover, such as pregnancy or osteoporosis. [16] Congenital lead poisoning may result from release of lead from bone stores accumulated by the mother through lead poisoning in her childhood [17]. Prolonged immobilization resulting in bone breakdown may increase blood lead levels [18].

LEAD AND CELL METABOLISM

Lead has an affinity for cell membranes and mitochondria [19,20]. It is a powerful enzyme inactivator and reduces mitochondrial oxidative phosphorylation in the target organs of lead poisoning: kidney, brain, and the hematopoietic system. Transmembrane transport may be affected by inhibition of sodium, potassium, and calcium ATPases [19]. Interaction of lead with calcium alters calcium metabolism by impairing the important intracellular messenger actions of calcium and altering endocrine, neural, and vasomotor functions [18,21]. Lead at picomolar concentrations stimulates brain protein kinase C, an important calcium-dependent enzyme that modulates critical intracellular regulatory and transport proteins by phosphorylation. Within the vasomotor system lead may antagonize calcium action on smooth muscle cells by affecting Ca ATPase [19].

SOURCES OF LEAD POISONING

Environmental sources

The major sources of lead for infants and children are dust and soil, chips of leaded paint, water, and food. Ingestion of lead-contaminated dust and soil by hand-to-mouth activity is the major source for most children but ingestion of leaded paint chips due to pica is still an important source of exposure. In houses built more than 20 years ago it is very likely that lead based paint was used. Heat guns and sanding create toxic lead fumes and lead dust that may be inhaled or ingested. If such home renovations have been performed without proper precautions, all family members should be tested. The relative importance of lead sources is different for infants less than a year than for the toddler age-group. Lead is
excreted into breast milk and mothers with high exposure may have increased breast-milk lead.

Herbal medicines and seemingly innocuous over the-counter food supplements may be high in lead [22]. Lead has been found as a major constituent of folk medicines used for colic or other gastrointestinal disorders, teething discomfort [23], fever [24], and skin rashes. Ayurveda, traditional Indian medicine, uses some products derived from metals and minerals, [23, 22] commonly lead and mercury. Lead poisoning from ayurvedic products had been reported in Asian Indians living in Vancouver [25], Montreal [23] and Los Angeles [22].

Source identification and control

The effects of lead exposure may be attributed to widespread contamination or to a local, focused source. For this reason, multiple sources (e.g., leaded gasoline, industrial processes, paint, solder in canned foods, water pipes, etc.) and pathways (air, household dust, street dirt, soil, water, and food) may all play a role. Any efforts to prevent lead poisoning must consider identifying and reducing children's exposures to all possible sources of lead. Some sources of lead that have been identified by epidemiologic investigations are described below.

Lead gasoline [air]

Automobiles that burn leaded gasoline are a major source of lead in air, dust and soil in many developing countries (UNEP and UNICEF, 1997). In large cities where leaded gasoline is still used, it accounts for 80 to 90 percent of airborne lead. Inspired by the successful U.S. phase-out of leaded gasoline and the concurrent decline in national BLLs, international health agencies (e.g., World Health Organization), national governments (e.g., India, Indonesia, Mexico) and major donor organizations (e.g., World Bank, U.S. Agency for International Development) have taken steps to stimulate the phase-out of lead in gasoline in other countries [26]. Studies in several large international cities have shown sharply reduced lead levels after initiating the phase-out of leaded gasoline.

Ceramic glazing [soil]

High lead levels were reported among children in a village in Ecuador where the primary occupation was producing lead-glazed ceramics [27]. The lead used in the process was extracted from discarded automobile batteries. Children lived, ate, and played near the lead glazing kilns.

Battery recycling [soil]

Battery recycling has been shown to be a significant source of lead in a number of studies. After the close of an auto battery recycling plant in 1997 in Haina, Dominican Republic, children who lived nearby were tested for lead poisoning. Considerable contamination of the area continued to expose children to lead dust. The exposed children's homes were located near the shops, and the children played and spent considerable time in the work area. These findings suggest that lead dust generated from the disassembly of batteries and the storage of battery parts can result in high blood lead levels in children [28].

Flour milling [food]

A report of an outbreak of gastrointestinal diseases in southern Egypt, an investigation revealed that these illnesses were caused by lead toxicity, and the source of the outbreak was flour contaminated with lead during the grinding process [29]. Flour is a diet staple, and each village in rural Egypt has at least one flour mill. Molten lead is frequently used to attach the grinding stone to the iron bar connected to the axle that rotates the grinding stone. As the grinding surface wears down from repeated use, lead is deposited in the flour. Preventive actions were taken in Egypt and other countries to improve maintenance of the flour mills and discontinue use of molten lead. However, although contaminated flour was first described as an important source of endemic lead poisoning in the Middle East almost 20 years ago, the use of lead in community flour mills has not been eliminated and continues to represent a significant environmental risk. [30] Similar mill practices have been observed in communities throughout Latin America and in parts of Asia.

Household [water]

Ground and surface water generally have low lead levels. Lead contaminates drinking water via lead based plumbing connectors, lead soldered joints and/or lead-containing brass faucets. Water that is low in mineral content (soft), acidic, and hot is more likely to leach lead; the time of standing in contact with lead piping or solder is also correlated with higher lead content. As estimated 16% of household water supplies have lead in excess of 20µg/L. Older water coolers in schools and public buildings also may contain lead solder, with resulting high water levels. Their intermittent use, with water standing for sometime may exacerbate this phenomenon. Elevated lead levels in infancy are associated with the use of hot tap water that has been further boiled down to prepare infant formula as has water boiled in an imported Iranian kettle [31].

Toxicology

Gastrointestinal (GI) absorption is less efficient than pulmonary absorption. Adults absorb an estimated 10-15% of ingested lead in food, and children have a higher GI absorption rate, averaging 40-50%. However, it should be noted that fasting and diets deficient in iron,
calciuim and zinc enhances GI absorption of lead, factors that are frequent among groups of young children. A study of adults under fasting conditions found a lead absorption rate from beverage consumption of almost 60%. The role of essential trace elements in decreasing lead absorption is assumed to be a consequence of competitive absorption processes; and iron-binding protein, mobilferrin, initially identified in rat duodenum, is also found in human duodenal mucosa and competitively binds lead. Cutaneous absorption of organic lead is low; one study found an average absorption of 0.06% through intact skin. Transplacental lead transfer is critical in fetal and neonatal lead exposure, which is under increasing scrutiny in recent years. Lead readily crosses the placental barrier throughout gestation, and lead uptake is cumulative until birth [32].

Distribution

Lead uptake into soft tissues occurs in a complex fashion that depends on numerous factors, including blood levels external exposure factors, specific tissue kinetics. In general, tissue lead content in populations without very excessive exposure averages 200–500 parts per billion (ppb); rises above this with excessive exposure rapidly produce over toxicity. For example, brain lead content in humans with overt encephalopathy is on the order of 1–2 ppm or less. BLLs of only 100–150 ppb (10–15 µg/dL) are now recognized as associated with subtle toxic effects in critical target organs. Lead in the CNS is of particular toxicologic importance, and studies have addressed specific tissue kinetics. In general, tissue lead content is found in hippocampus, cerebellum, cerebral cortex, and medulla [31].

Excretion

A miniscule amount is lost via sweat, hair, and nails. Children excrete less of their daily uptake than adults with an average retention of 33% versus 1–4% respectively. Biologic half lives for lead are as follows: Blood (adults, shorter experiments), 25 days; blood blood (children, natural exposure), 40 days; bone (labile, trabecular pool), 90 days; and bone (cortical, stable pool), 10–20 years. Tetraethyl lead is lipid soluble, easily absorbed through intact skin and distributed widely to lipophilic tissues including the brain. Tetraethyl lead is metabolized to triethyl lead, which is believed to be the major toxic compound. Alkyl leads may slowly release lead as the inorganic form, with subsequent kinetics as noted above [31].

MANAGEMENT OF LEAD POISONING

BAL (British anti-lewisite)

Mechanism of action

Two molecules of BAL combine with one atom of heavy metal to form a stable complex. BAL enhances fecal as well as urinary excretion of lead and diffuses well into erythrocytes. It can be administered in the presence of renal impairment because it is predominantly excreted in bile.

Route of administration and dosage

BAL is available only in oil for intramuscular administration. It must be given every 4 hours.

Toxicity

Mild febrile reactions may occur, and transient elevation of hepatic transaminase activities may be observed. Other minor adverse effects include, in order of frequency, nausea and occasional vomiting, headache, mild conjunctivitis, lacrimation, rhinorrhea, and salivation. Most side effects are transient and rapidly subside as the drug is metabolized and excreted.

Precautions

In patients with G-6-PD deficiency, BAL should be used only in life-threatening situations, because it may induce hemolysis. Medicinal iron should never be administered during BAL therapy, because the combination is very toxic. If iron deficiency coexists, its management should be postponed until BAL therapy is concluded. In cases of extreme anemia blood transfusions are preferable.

CaNa2-EDTA

Only CaNa2-EDTA (calcium disodium versenate) should be used for treatment of lead poisoning. Na2-EDTA (endrate disodium) should never be used for treatment of lead poisoning, because it may induce fatal hypocalcemia and tetany.

CaNa2-EDTA increases urinary lead excretion 20– to 50-fold. CaNa2-EDTA does not enter the cells; thus it removes lead from the extracellular compartment. Indirectly, lead is reduced in the soft tissue, central nervous system, and red blood cells.

Route of administration and dosage

CaNa2-EDTA may be given intravenously or intramuscularly. The preferred and most effective route is a continuous intravenous infusion; a given dose is most effective if infused over 6 hours. CaNa2-EDTA should be diluted to a concentration <0.5% in dextrose and water or 0.9% saline solution. When administered intravenously as a single dose, it should be similarly diluted and administered by slow infusion over 15 to 20 minutes. Intramuscular administration of CaNa2-EDTA is extremely painful and should be given with procaine (0.5%) by deep injection. CaNa2-EDTA should not be
given orally, because it may enhance absorption of lead from the gastrointestinal tract.

Dosages vary in different situations and are discussed below. In all cases, courses should be limited to 5 days, followed by at least 2 to 5-day intervals to allow recovery from zinc depletion.

**Toxicity**

The renal toxicity may be reduced by assuring adequate diuresis. CaNa$_2$-EDTA should never be given in the absence of an adequate urine flow. Before administering it intramuscularly in children in good clinical condition, adequate oral intake of fluids must be assured.

**Precautions**

During chelation with CaNa$_2$-EDTA, urine and its sediment, BUN, serum creatinine, and liver function tests must be carefully monitored. The appearance of protein and formed elements in urinary sediment, and rising BUN and serum creatinine values signify impending renal failure, the serious toxicity associated with excessive or prolonged administration of EDTA.

**Penicillamine**

D-Penicillamine is not licensed by the Food and Drug Administration for the treatment of lead poisoning. Its use for this indication is thus to be considered experimental. It is the only commercially available oral chelating agent. It can be given over a long period (days). Toxic side effects may occur in as many as 20% of patients given the drug.

**Mechanism of action**

D-Penicillamine enhances urinary excretion of lead, although not as effectively as CaNa$_2$-EDTA. Its specific mechanism of action is not well understood.

**Route of administration and dosage**

D-Penicillamine is administered orally. It is currently available in capsules (125 and 250 mg). These capsules may be opened and suspended in liquid, if necessary. The usual dose is 30 mg/kg.

**Side effect**

Side effect can be minimized by initiating therapy with small doses, for example, 25% of the desired final dose, increased after 1 week to 50% and again after 1 week to the full dose, while monitoring for possible toxicity.

**Toxicity**

The main side effects of D-penicillamine are reactions resembling those of penicillin sensitivity, including fevers, rashes, leukopenia, thrombocytopenia, and eosinophilia.

**New agents**

Dimercaptosuccinic acid and 2-3-dimercapto-propane-1-sulphonate are both water-soluble derivatives of BAL. Although both appear promising and safe and have been used successfully in treatment of other heavy-metal poisoning, these drugs are presently in the investigative stage for the treatment of lead poisoning.

**Acute lead encephalopathy**

Acute lead encephalopathy is characterized clinically by some or all of the following symptoms: coma, seizures, bizarre behavior, ataxia, apathy, incoordination, vomiting, alteration in the state of consciousness, and subtle loss of recently acquired skills. Any one or a matrix of these symptoms associated with an elevated blood lead concentration constitutes an acute medical emergency. Lead encephalopathy is almost always associated with a blood lead concentration >100 µg/dl, although it has been reported at blood lead levels as low as 70 µg/dl.

**GENERAL SUPPORTIVE MANAGEMENT**

All oral intake is prohibited initially until the child's condition has significantly improved. Parenteral fluid therapy is begun immediately; volume is restricted to basal requirements plus a careful assessment of continuing losses. Excessive intravenous fluid administration must be avoided. Once urine flow is established by administering dextrose in water (10 to 20 ml/kg body weight), chelation treatment, already begun with BAL alone for one dose, is continued with simultaneous administration of CaNa$_2$-EDTA. An adequate flow of urine must be established before intravenous chelation therapy. Parenteral fluid therapy minimizes vomiting that may accompany administration of BAL and ensures prompt excretion of CaNa$_2$-EDTA, a drug excreted exclusively by the kidney. For initial control of seizures, diazepam or paraldehyde is the preferred drug. Barbiturate and phenytoin are reserved for the long-term management of recurring seizures, only after the acute episode is managed and consciousness has been fully recovered. Although it is desirable to evacuate any residual lead from the bowel, this should not delay the start of chelation therapy. Surgical decompression and hypertonic solutions to relieve intracranial pressure and cerebral edema are contraindicated. The diagnosis of acute lead encephalopathy can usually be made without lumbar puncture, which is extremely risky because of the presence of increased intracranial pressure. In fulminating lead encephalopathy, increased intracranial pressure may be present in the absence of any of the usual preliminary signs (changes in blood pressure, pulse or respiration, retinal hemorrhage or edema). If examination of the CSF is absolutely essential for the differential diagnosis, the very least amount of fluid, not exceeding a few drops, should be carefully obtained.
CHELATION THERAPY
Treatment is begun with a priming dose of 75 µg/ml BAL only, given by deep intramuscular injection; BAL is administered at a dose of 450 µg/ml/24 hours, in divided doses of 75 mg/ml every 4 hours. Once the priming dose is given and an adequate urine flow is established, administration of CaNa2-EDTA is begun at a dose of 1500 mg/ml/24 hours. CaNa2-EDTA is given by continuous intravenous drip in dextrose and water or 0.9% saline solution. The concentration of CaNa2-EDTA should not exceed 0.5% in the parenteral fluid. (In the treatment of acute encephalopathy, restriction of parenteral fluids takes precedence, so that CaNa2-EDTA may have to be given intramuscularly if fluid overload is to be avoided.) Combined BAL-CaNa2-EDTA therapy is given for a total of 5 days. During treatment, renal and hepatic function and serum electrolyte levels should be monitored daily.

A second course of chelation therapy with CaNa2-EDTA alone or with BAL, depending on the blood lead concentration, may be required after a 2-day interval. A third course is required only if the blood lead concentration rebounds to a value >50 µg/dl within 48 hours after treatment. Unless there are compelling clinical reasons, it is desirable to wait at least 5 to 7 days before beginning a third course of CaNa2-EDTA.

SYMPTOMATIC LEAD POISONING WITHOUT ENCEPHALOPATHY
Symptomatic lead poisoning without encephalopathy is characterized by one or several of the following symptoms: decrease in play activity, lethargy, anorexia, sporadic vomiting, intermittent abdominal pain, and constipation. Symptomatic lead poisoning is usually associated with a blood lead concentration >70 µg/dl, although occasionally may be associated with a blood lead concentration as low as 50µg/dl. If the blood lead concentration is <50 µg/dl, other diagnostic possibilities should be vigorously sought. Because all symptomatic children potentially have acute lead encephalopathy, treatment and supportive measures must be instituted immediately on an emergency basis.

GENERAL SUPPORTIVE MANAGEMENT
All oral intake is prohibited and the guidelines of parenteral fluid therapy are followed as noted above for the treatment of lead encephalopathy. Intravenous fluids are given at a rate consistent with basal requirements plus ongoing losses. Excessive fluid administration must be avoided.

Chelation therapy
Treatment is begun with a priming dose of 50 mg/ml BAL by deep intramuscular injection; BAL is administered at a dose of 300 mg/ml/24 hours in divided doses of 50 mg/ml every 4 hours. Once the priming dose is given and an adequate urine flow is established, administration of CaNa2-EDTA is begun at a dose of 1000 mg/ml/24 hours. CaNa2-EDTA is given by continuous intravenous drip in dextrose and water or 0.9% saline solution. Although continuous infusion of CaNa2-EDTA is preferable, it may be replaced by doses of 175 mg/ml every 4 hours, given either intravenously over 15 to 20 minutes through a heparin lock or by deep intramuscular injection mixed with procaine. The concentration of CaNa2-EDTA should not exceed 0.5% in the parenteral fluid. Combined BAL-CaNa2-EDTA therapy is given for a total of 5 days. During treatment, renal and hepatic function and serum electrolyte levels should be monitored daily. It is advisable to measure the blood lead concentration daily. (It will be necessary to interrupt the CaNa2-EDTA infusion for 1 hour before this sample is obtained, to avoid a spuriously high value). If the blood lead concentration reaches <50 µg/dl, as it may within 3 days of combined BAL and CaNa2-EDTA therapy, BAL may be safely discontinued and CaNa2-EDTA continued for a full 5-day course of treatment. If measurements of blood lead cannot be obtained in time, it is safe to continue BAL for the full 5-day course. Except under highly unusual circumstances, CaNa2-EDTA should not be administered for more than 5 consecutive days.

A second course of chelation therapy may be required after a 2 to 4 day interval, to be started with CaNa2-EDTA alone or with concomitant BAL, depending on the blood lead concentration. A third course may be required if the blood lead concentration rebounds to a value >50 µg/dl within 7 to 10 days after treatment. Unless there are compelling clinical reasons, it is highly desirable to allow 5 to 7 days before beginning a third course of CaNa2-EDTA.

CaNa2-EDTA PROVOCATION TEST
First, a repeated baseline blood lead level is obtained and the patient is asked to empty the bladder. Then CaNa2-EDTA is administered at a dose of 500 mg/ml intravenously in 250 ml of 5% dextrose, infused over 1 hour. (A painful but practical alternative is to administer the same dose intramuscularly mixed with procaine and to encourage the child to drink as much as possible in the first 2 hours). All urine must be collected with lead-free equipment over 8 hours. The urine volume should be carefully measured, and aliquots should be sent to the laboratory for measurement of the concentration of lead. Extreme care should be exercised to use only lead-free equipment. If this is not available in the clinic, it may be best that the entire urine volume be sent to on positive findings of a carefully performed CaNa2-EDTA provocation test.

Immediate treatment follow-up
The goal of chelation therapy is to permanently reduce the blood lead level to <25 µg/dl and that of EP to <35 µg/dl. To achieve this goal it may be necessary to give several courses of treatment. It cannot be overemphasized, however, that repeated courses of therapy are counterproductive unless the source of lead has been identified and eradicated. Children receiving chelation therapy should not be released from the hospital until all lead hazards in their homes and elsewhere have been controlled and eliminated and, if necessary, suitable alternative housing has been arranged. With vigorous public health measures complete and safe abatement should be achieved during the treatment period. If a child with elevated blood lead concentration cannot be moved to new housing, multiple repeated courses of CaNa2-EDTA in a clinically asymptomatic child with stable blood lead values may be counterproductive; parents may despair at the ineffectiveness of therapy and fail to return to the clinic. It is more important in these unfortunate situations to maintain follow-up so that a rise in blood lead concentrations is detected promptly. At the end of each treatment cycle the blood lead concentration usually declines to values <25 µg/dl. However, within a few days reequilibration takes place and results in a rebound; thus the blood lead level must be rechecked 7 to 10 days after the end of treatment. If the blood lead level rebounds to within 5 µg/dl of the value before the last cycle, additional treatment cycles are indicated (unless the concentration after rebound is <25 µg/dl). A blood lead concentration that rebounds to above the pre-treatment value is evidence of renewed and excessive intake. If the blood lead level remains low, its measurement must be repeated, initially biweekly, then at monthly intervals, to assure that the decreased level is permanent. Iron deficiency states, which may accompany lead poisoning, require therapeutic doses of iron in addition to the correction of other possible nutritional deficiencies.

Long-term clinical follow-up and management

Commonly this can be accomplished best if children with lead poisoning are referred for long-term follow-up to a special clinic where all phases of clinical management can be coordinated and continuity of care is maintained. At the outset, a long-term plan of management is developed. Adults who work in lead industries must shower before coming home and must leave all work clothes, including shoes, at the work place; these clothes must not be cleaned or washed at home. Thus lead-bearing diast from the place of employment will not contaminate the house. Additional sources may include old lead-painted cribs and beds and the burning of lead-painted wood in wood-burning stoves. Proximity to lead smelters, ingestion of lead-containing dust, and inhalation of lead from the combustion of gasoline contribute to the overall body burden of lead in children, but the high Concentration of lead that ultimately results in clinical lead poisoning is most frequently associated with ingestion of lead-bearing paint. Uncommon causes of poisoning include ingestion and retention in the stomach of metallic lead (fishing weights, curtain weights, shot, jewellery painted with lead to simulate pearl), Contamination of acidic foods and beverages from improperly lead-glazed ceramic pitchers, pots, and cups and from opened lead-soldered food cans, and the home burning of battery casings. Inhalation of fumes (sniffing) from small leaded-gasoline containers has occurred in older children. Poisoning has also been traced to oriental cosmetics (surma, a black eyeliner containing up to 85% lead) and to Mexican and Oriental folk remedies (azarcon, greta, paylooaah).

Medical management during abatement of lead paint hazards

If the source of lead is limited to such items as retention of a metallic lead object in the stomach or an improperly lead, glazed food or beverage container, the child can be promptly separated from the source. Such is not the case when lead paint in the home is the principal source. Several methods are used to remove old lead-based paint from walls and woodwork. Some methods, particularly removal by burning and sanding, greatly increase the amount of air and dust borne lead in the home. Very fine lead-bearing particulates settle out slowly over many hours after burning and sanding is completed. It is of the utmost importance to remove all young children and pregnant women from a dwelling until the abatement process is completed. They should live elsewhere day and night, and should not return until removal of all lead-bearing paint has been completed and the dwelling has been thoroughly vacuumed and scrubbed with high-phosphate-detergent solutions. The sources that have been denuded during the abatement process should be repainted to seal any residual lead behind the surface. Children should be removed from the home during abatement whether or not they have increased lead absorption. When this procedure is not followed, it is not uncommon to observe 30 to 50 µg/dl increments in whole blood lead concentration within a matter of a few days or weeks.

Long-range dust control

It must be understood that dust control is not a substitute for abatement. In areas heavily contaminated with lead, such as deteriorating old housing or heavy vehicular traffic, it may be helpful to institute a regular program in and about the home to control lead-bearing dust. Which constantly re-accumulates.

Because hand-to-mouth activity is common in young children, parents must institute a specific type of cleaning program; vacuuming and wet cleaning are recommended. Sweeping with a broom, although it may remove large fragments, serves only to stir up smaller
particulates. It is recommended that all floors and woodwork be scrubbed weekly with high-phosphate detergents such as Tide or Spic and Span. For all surfaces that the child can touch, the weekly scrubbing should be supplemented with daily damp dusting with a cloth rinsed in a solution of high phosphate detergent. Although such cleaning programs may be helpful, the definitive way to prevent recurrences is for affected children and their families to move into housing free of lead paint hazards.

**Dietary factors**

Although reduction in exposure to environmental lead must receive first priority, steps should be taken to identify and correct deficient dietary intake, particularly of calcium and iron as well as excessive dietary fat. Each of which may increase the absorption and retention of lead. A diet adequate in minerals and limited in fat should be assured. For those intolerant of cow milk, lactose-free milk products such as yogurt or some alternative source are necessary to ensure adequate calcium intake. The use of low-fat milk and the avoidance of fried foods should limit excessive dietary fat. Acidic foods such as fruits, fruit juices, tomatoes, sodas, "and cola drinks may leach lead from cans with leaded-soldered seams. Dietary lead intake may be reduced if the above items are purchased fresh, frozen, or packaged in aluminum, glass, cardboard, or plastic containers. [33]

**Autopsy feature**

1. Pale skin, conjunctivae and mucosa (anaemia)
2. Emaciation
3. Burtonian line
4. Lead lines on X-ray
5. Pathological lesions or changes are sometimes found in kidney, liver, male gonads, nervous system, blood vessels.[34]

### Blood Lead Levels Associated with Adverse Health Effects

<table>
<thead>
<tr>
<th>Children</th>
<th>Lead Concentration in Blood (µg/dL)</th>
<th>Adults</th>
</tr>
</thead>
</table>
| Death    | 150                                 | Encephalopathy  
Nephropathy |
| Encephalopathy  
Nephropathy  
Frank Anemia  
Colic | 100                                 | Frank Anemia  
Male Reproductive Effects  
↓Hemoglobin Synthesis and Female Reproductive Effects |
| ↓Hemoglobin Synthesis  
↓Vitamin D Metabolism  
↓Nerve Conduction Velocity | 50                                 | ↓Nerve Conduction Velocity  
Elevated Blood Pressure  
↑Erythrocyte Protoporphyrin (men)  
↑Erythrocyte Protoporphyrin (women) |
| ↓Nerve Conduction Velocity  
↑Erythrocyte Protoporphyrin  
↓Vitamin D Metabolism(?)  
Developmental Toxicity  
↓IQ, ↓Hearing, ↓Growth | 40                                 | ↓Nerve Conduction Velocity  
Elevated Blood Pressure  
↑Erythrocyte Protoporphyrin (men)  
↑Erythrocyte Protoporphyrin (women) |
| ↓Vitamin D Metabolism  
↓Nerve Conduction Velocity | 30                                 | ↓Nerve Conduction Velocity  
Elevated Blood Pressure  
↑Erythrocyte Protoporphyrin (men)  
↑Erythrocyte Protoporphyrin (women) |
| ↓Nerve Conduction Velocity | 20                                 | ↓Nerve Conduction Velocity  
Elevated Blood Pressure  
↑Erythrocyte Protoporphyrin (men)  
↑Erythrocyte Protoporphyrin (women) |
| ↓Nerve Conduction Velocity  
↑Erythrocyte Protoporphyrin  
↓Vitamin D Metabolism(?)  
Developmental Toxicity  
↓IQ, ↓Hearing, ↓Growth | 10                                 | ↓Nerve Conduction Velocity  
Elevated Blood Pressure  
↑Erythrocyte Protoporphyrin (men)  
↑Erythrocyte Protoporphyrin (women) |

**Note:** ↑= increased function and ↓= decreased function.  
**Source:** ATSDR, 1992  
**Courtesy to Pamela A. Meyer 2008**
Table 1. Representative lead compounds [6]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Formula</th>
<th>Major Use/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead arsenate</td>
<td>Pb₃(AsO₄)₂</td>
<td>Insecticide</td>
</tr>
<tr>
<td>Lead azide</td>
<td>Pb(N₃)₂</td>
<td>Cartridge primers, Primer cord</td>
</tr>
<tr>
<td>Lead carbonate</td>
<td>2PbCO₃(Pb(OH))₂</td>
<td>Paint pigment (Chrome yellow)</td>
</tr>
<tr>
<td>Lead oxide</td>
<td>Pb₃O₄</td>
<td>Paint pigment (red lead) commonly used as primer for rust protection of metal. Other oxides used as pigments and in glazes</td>
</tr>
<tr>
<td>Lead silicate</td>
<td>PbSiO₃</td>
<td>Glazes for china, Porcelain, titles</td>
</tr>
<tr>
<td>Lead sulphide</td>
<td>PbS</td>
<td>Most abundant lead ore (galena): responsible for gingival lead line</td>
</tr>
<tr>
<td>Tetraethyl lead</td>
<td>Pb(C₂H₅)₄</td>
<td>Antiknock additive to gasoline</td>
</tr>
</tbody>
</table>

Table 2. Current CDC management recommendations [8]

<table>
<thead>
<tr>
<th>Blood lead level (mg/dL)</th>
<th>Actions</th>
<th>Time frame for beginning intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>10–14</td>
<td>Provide care giver lead education. Provide follow up testing. Refer the child for social services if necessary</td>
<td>Within 30 days</td>
</tr>
<tr>
<td>15–19</td>
<td>Above actions, plus: if BLLs persist (i.e., two venous BLLs in this range at least 3 months apart) or increase, proceed according to actions for BLLs</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>20–44</td>
<td>Above actions, plus: provide coordination of care (case management). Provide clinical evaluation and care. Provide environmental investigation and control current lead hazards</td>
<td>Within 1 week</td>
</tr>
<tr>
<td>45–70</td>
<td>Above actions</td>
<td>Within 48 hrs</td>
</tr>
<tr>
<td>70 or higher</td>
<td>Above actions, plus hospitalize child for chelation therapy immediately</td>
<td>Within 24 hrs</td>
</tr>
</tbody>
</table>

Table 3. Potential risk factors for lead poisoning

<table>
<thead>
<tr>
<th>Socio-demographic</th>
<th>Residential</th>
<th>Occupational (home, work place and neighbourhood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Use of canned foods or drinks</td>
<td>Working with cars</td>
</tr>
<tr>
<td>Sex</td>
<td>Use of ceramic bowls or food storage container</td>
<td>Recycling batteries</td>
</tr>
<tr>
<td>House hold expenses</td>
<td>Use of cosmetic by children in household</td>
<td>Making cement (bridge, tunnel constructions)</td>
</tr>
<tr>
<td>Level of education of</td>
<td>Use of folk medicine (alcohol, azarcon, baligoli, ghazard, greta, pay-loo-ah, koosar)</td>
<td>Working as a gas station attendant</td>
</tr>
<tr>
<td>primary care giver in</td>
<td>Location of the house with respect to traffic</td>
<td>Making jewellery with lead solder</td>
</tr>
<tr>
<td>household</td>
<td>-highway or major intersection(heavy traffic)</td>
<td>Making plastics</td>
</tr>
<tr>
<td>-none</td>
<td>-street with moderate to heavy traffic</td>
<td>Making or glazing ceramics</td>
</tr>
<tr>
<td>-primary</td>
<td>-street with little traffic</td>
<td>Priting</td>
</tr>
<tr>
<td>-secondary</td>
<td>Whether or not house is painted</td>
<td>Recycling metals( other than lead)</td>
</tr>
<tr>
<td>-college or higher (reference)</td>
<td>-yes</td>
<td>Foundry worker</td>
</tr>
<tr>
<td>Numbers of people living in household</td>
<td>-no</td>
<td>Firing range work</td>
</tr>
<tr>
<td>Floor type in home (dirt, cement, tile, wood, other)</td>
<td>If the house is painted, how it is painted (i.e. Inside, outside, both)</td>
<td></td>
</tr>
<tr>
<td>Smoking by household member</td>
<td>Whether paint in household is peeling</td>
<td></td>
</tr>
<tr>
<td>Primary water collection method</td>
<td>-well water</td>
<td></td>
</tr>
<tr>
<td>-other</td>
<td>-piped</td>
<td></td>
</tr>
<tr>
<td>Firing range work</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Environmental lead sources

<table>
<thead>
<tr>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead paint</td>
<td>Especially pre-1978 homes</td>
</tr>
<tr>
<td>Dust</td>
<td>House dust from deteriorated lead paint</td>
</tr>
<tr>
<td>Soil</td>
<td>From yards contaminated by deteriorated lead paint, lead industry emissions, roadways with leaded gasoline usage</td>
</tr>
<tr>
<td>Water</td>
<td>Leached from leaded plumbing (pipes, solder), cooking utensils, water coolers</td>
</tr>
<tr>
<td>Air</td>
<td>Leaded gasoline industrial emissions</td>
</tr>
<tr>
<td>Food</td>
<td>Lead solder in cans; “natural” calcium supplements “moonshine” whiskey; lead-foil covered wines; contaminated flour, paprika.</td>
</tr>
<tr>
<td>Exotic</td>
<td>Folk remedies, cosmetics; ingested lead foreign bodies, retained lead bullets; illicit substance abuse (heroin, methamphetamine, leaded gasoline “huffling”) burning batteries, leaded paper or wood for fuel; use of lead glazed ceramics; hand-mouth contact with pool cue chalk, glazes, leaded ink; vinyl miniblinds.</td>
</tr>
</tbody>
</table>

CONCLUSION

Our review shows that point of care in management of lead poisoning in paediatrics and geriatrics population. Despite intensive clinical and scientific investigation of lead poison, attempts to improve its management and to develop targeted drug therapy have not yielded a clear breakthrough. Reorganisation of delivery of care to treat lead poisoning cases in rural and urban population. Assessment of the effectiveness of public health strategies will be important to identify specific pathways that can be effectively targeted to treat lead poison the timing and dosing of antidote, when it’s effective.

REFERENCES

4. Pillai VV. Comprehensive Medical toxicology 2nd edition Paras publication 119-120.
8. Adapted from Managing Elevated Blood Lead Levels Among Young Children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention, CDC, 2002.