LEAD: ITS DETECTION, SPECIFICATION AND TOXICITY

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ABSTRACT

Lead is a heavy metal used in pharmaceutical industry in a few quantity but small alteration in the quantity may cause a toxic and hazardous effect on the human health. Lead in pharmaceutical industry is used very cautiously and its quantity and quality is determined accurately. The Indian pharmacopoeia specifies a number of specification for the lead used in pharmaceutical industry. The following article covers all the specification according to the Indian pharmacopoeia and british pharmacopoeia. The article describes all the toxicity related to lead affecting organs and its treatment. Various chelating agent used for the treatment of lead poisoning are also covered in this article.

KEYWORDS: Pharmaceutical, hazards, toxicity, EDTA.

INTRODUCTION

Pure lead (Pb) is a heavy metal at room temperature and pressure. A basic chemical element, it can combine with various other substances to form numerous lead compounds.[1] Lead poisoning is one of the oldest, permanent hazards in the world and Iran is not excluded and has the same risk of lead toxicity. Humans have known about the potential hazards of lead poisoning for centuries. Lead is wide spread in natural substances, and almost all people are in touch with this insidiously toxic heavy metal indifferent ways either in workplace or at homes. Employees of paint factories, workers of copying centers, bus drivers, and tile making factories are in higher risk of lead toxicity. The problem would be worse if we consider that even foods have high concentration of lead, for examples vegetables, powdered milk, bread, machine made lemon juice and tomato paste, peanut, raw milk and black tea as well as
many fishes from Caspian sea, Persian gulf, and farmed fishes may have higher levels of lead.\cite{2}

**SOURCES OF LEAD IN PHARMACEUTICAL INDUSTRY\cite{3}**

<table>
<thead>
<tr>
<th>Lead Source</th>
<th>Contaminated Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead solder/pipes</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Packages or storage containers</td>
<td>Food, beverages</td>
</tr>
<tr>
<td>Paint (pre-1978)</td>
<td>Household dust and soil</td>
</tr>
<tr>
<td>Production sources</td>
<td>Imported foods, remedies, cosmetics, jewelry</td>
</tr>
<tr>
<td>Mining and smelting</td>
<td>Outdoor air and dust</td>
</tr>
<tr>
<td>Workplaces involving lead</td>
<td>Outdoor and indoor air and dust</td>
</tr>
<tr>
<td>Gasoline (pre-1988)</td>
<td>Soil</td>
</tr>
</tbody>
</table>

**PRESCRIBED AMOUNT OF LEAD IN PHARMACEUTICAL COMPOUNDS**

The standard establishes maximum limits of exposure to lead for all workers covered, including a permissible exposure limit (PEL) and action level (AL). The PEL sets the maximum worker exposure to lead: 50 micrograms of lead per cubic meter of air (50μg/m3) averaged over an eight-hour period. If employees are exposed to lead for more than eight hours in a workday, their allowable exposure as a TWA for that day must be reduced according to this formula.

\[
\text{Employee exposure (in } \mu\text{g/m}^3\text{)} = \frac{400}{\text{hours worked in the day}}. \]

**LEAD TOXICITY**

Lead (Pb) is ubiquitous and one of the earliest metals discovered by the human race. Unique properties of lead, like softness, high malleability, ductility, low melting point and resistance to corrosion, have resulted in its widespread usage in different industries like automobiles, paint, ceramics, plastics, etc. This in turn has led to a many fold rise in the occurrence of free lead in biological systems and the inert environment. Lead is regarded as a potent occupational toxin and its toxicological manifestations are well known. The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment. Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelting and coal combustion, lead-based paints, lead containing pipes or lead-based solder in water supply systems, battery recycling, grids and bearings, etc. Although lead toxicity is a highly explored and comprehensively published topic, complete control and prevention over lead exposure is still far from being achieved.\cite{5}

Most heavy metals are not physiologically or biochemically essential to an organism. In
many cases they are extremely dangerous, as they are easily absorbed and remain in tissues for a long time. Heavy metals become toxic when they are not metabolized by the body and accumulate in the soft tissues. The toxicity of metals changes with their form, solubility, and ability for transformation.\textsuperscript{[6]}

**Determination of lead in blood**

- The Centers for Disease Control and Prevention recommends blood lead testing for all refugee children who are 6 months to 16 years old upon entering the United States.
- Unlike U.S. children, studies indicate that age is not a significant risk factor for elevated Blood lead level (BLLs) among refugee children.
- Repeat BLL testing of all refugee children who are 6 months to 6 years of age, 3 to 6 months after they are placed in permanent residences, should be considered a “medical necessity,” regardless of initial test result.\textsuperscript{[7]}

**HAZARDS DUE TO LEAD**

Lead in the body is distributed to the brain, liver, kidney and bones. It is stored in the teeth and bones, where it accumulates over time. Human exposure is usually assessed through the measurement of lead in blood. Lead is a naturally occurring toxic metal found in the Earth’s crust. Its widespread use has resulted in extensive environmental contamination, human exposure and significant public health problems in many parts of the world. Important sources of environmental contamination include mining, smelting, manufacturing and recycling activities, and, in some countries, the continued use of leaded paint and leaded gasoline. More than three quarters of global lead consumption is for the manufacture of lead-acid batteries for motor vehicles. Lead is, however, also used in many other products, for example pigments, paints, solder, stained glass, crystal vessels, ammunition, ceramic glazes, jewellery, toys and in some cosmetics and traditional medicines. Drinking water delivered through lead pipes or pipes joined with lead solder may contain lead. Much of the lead in global commerce is now obtained from recycling.\textsuperscript{[8]}

Some of the common symptoms include with lead poisoning Loss of appetite; Constipation; Nausea; Excessive tiredness; Headache; Fine tremors; Colic with severe abdominal pain; Metallic taste in the mouth; Weakness; Nervous irritability; Hyperactivity; Muscle and joint pain or soreness; Anxiety; Pallor; Insomnia; Numbness; and Dizziness.\textsuperscript{[9]}
Health Risks To Children

The Center for Disease Control estimates that nearly two million American children under the age of six have at least low-level lead poisoning. The CDC also estimates that 10% of all children suffer from lead poisoning. Even children who appear to be healthy can have high levels of lead in their bodies. Children are usually lead poisoned by ingesting the invisible lead-contaminated dust through normal hand-to-mouth activity. A small child may eat paint chips or soil that contains lead. Children also are likely to place their hands or other objects covered with lead-contaminated dust into their mouths. They can breathe in lead-contaminated dust, especially during renovations that disturb painted surfaces. Lead poses a more serious threat to children than to adults because their growing bodies absorb more lead than adult's bodies, and their brains and nervous systems are more sensitive to the damaging effects of lead. The blood lead level of concern is 10 µg/dl or greater.

Blood lead levels in children of 100 to 150 µg/dl are associated with swelling of the brain, resulting in severe brain damage and even death. Lead exposures this high in the United States are relatively rare today; however, these levels are encountered in industrialized countries that are not controlling lead exposures.

At low exposures, the effects of childhood lead poisoning can include

| impaired growth | headaches |
| hearing loss | impaired short-term memory |
| behavior problems* | |

* Such as attention deficit hyperactivity disorder (ADHD).

Health Risks To Adults

Lead poisoning in adults occurs most often to those exposed to lead-contaminated dust in lead related jobs and hobbies. At high levels, the lead can have an adverse effect on various nerves, such as the motor nerves. This damage can result in the inability to maintain the hand or foot in a normal position due to weakness of muscle tone because of nerve damage ("wrist drop" or "foot drop"). According to a recent study, long-term exposure to lead is linked to an increased risk of hypertension in men. A second study published in the same issue suggests that low-level lead exposure impairs kidney function in middle-aged and older men.

Additional effects of prolonged lead exposure in adults can include.

| respiratory problems | digestive problems |
| nerve disorders | memory loss |
| reproductive disorders | difficulties during pregnancy |
Health Risks To Pregnancies

Approximately 4.4 million, or 9 percent, of U.S. women of childbearing age have elevated blood lead levels. Lead, which is stored in the bones, moves out of the bones with calcium. If a woman was previously exposed to lead, the lead stored in her body may be released at an accelerated rate as calcium moves from her body to the unborn child, especially if her diet is calcium-deficient.

The tissues of the unborn baby can absorb lead as the infant develops in the womb. The developing brain is extremely vulnerable to the harmful effects of lead during this time. Due to the fact that lead can pass through the placenta to the fetus, a pregnant woman exposed to lead can place her unborn child at an increased risk of:

- low birth weight
- learning disabilities
- birth defects
- premature birth
- miscarriage
- still birth

Health Risks To The Elderly

Lead moves in and out of the bones with calcium, an essential nutrient for body cells. When calcium intake is insufficient, due to dietary deficiencies or hormonal changes, bones release the stored lead along with calcium. Osteoporosis intensifies the mobilization of lead stored in the bones, placing the elderly who have previously been exposed to lead at risk of suffering the effects of lead poisoning.\(^{[10]}\)

**DIAGNOSIS**

Laboratory tests

- Whole blood lead levels.
- \(<10 \mu g/dL\) - normal.
- \(>10 \mu g/dL\) - may cause impaired cognitive development in children.
- \(>45 \mu g/dL\) - GI symptoms in adults and children.
- \(>70 \mu g/dL\) - high risk of acute CNS symptoms.
- \(>100 \mu g/dL\) - may be life-threatening.\(^{[11]}\)

**Limit Test for Lead**

**Principle:** The limit test for lead is based on the reaction between lead and diphenyl thiocarbazone (dithizone) in an alkaline medium to form lead–dithiazonate complex. The lead present as an impurity in the substance is separated by extracting an alkaline solution with
dithizone extraction solution. The interference by other metal ions is eliminated by adjusting the optimum pH for the extraction by using reagents like ammonium citrate, potassium cyanide and hydroxylamine hydrochloride.

The original colour of dithizone in chloroform is green while the lead-dithiazonate complex is violet in colour. The intensity of the violet colour of the complex depending upon the quantity of lead present in the solution is compared with that of standard colour produced by treating standard solution containing definite amount of lead in the similar manner.

\[
\text{S} = \text{C}\begin{array}{c}
\text{NH.NHC}_6\text{H}_5 \\
\text{N=N.C}_6\text{H}_5
\end{array} + \text{Pb} \\
\text{Lead Dithizone Lead dithizonate complex}
\]

**Method (I.P. 2007):** Prepare the sample as directed in the monograph and transfer to a separator. Unless otherwise directed in the monograph, add 6 ml of ammonium nitrate solution and 2 ml hydroxylamine hydrochloride solution. To this, add two drops of phenol red solution and make the solution alkaline (red in colour) by adding strong ammonia solution. If necessary, cool the solution and add 2 ml of potassium cyanide solution. Immediately extract the solution with 5 ml portions of dithizone extraction solution, until it retains green colour. Combine the dithizone extracts and transfer to a second separator. Shake the combined dithizone extracts for 30 seconds with 30 ml of 1% v/v nitric acid solution and discard the chloroform layer. To the nitric acid solution, add exactly 5 ml of dithizone standard solution and shake for 30 seconds. The violet colour of the chloroform layer should not be more intense than that obtained by treating a volume of standard lead solution (1 ppm Pb) equivalent to the amount of lead permitted in the substance being examined in the same manner as that of solution being examined.

**Preparation of standard lead solution (1 ppm Pb):** Dissolve 0.400 g of lead nitrate in water containing 2 ml of dilute nitric acid and add sufficient water to produce 250.0 ml. This gives standard lead solution (1% Pb). Standard lead solution (1 ppm Pb) is prepared by diluting 1 volume of standard lead solution (1% Pb) to 1000 volumes with water.
Preparation of dithizone extraction solution: Dissolve 30 mg of dithizone in 1000 ml of chloroform and add 5 ml of ethanol (95%). The solution is stored in refrigerator. Before use, the solution is shaken with about half of its volume of 1% v/v nitric acid solution and acid is discarded.

Preparation of Dithizone standard solution: Dissolve 10 mg of dithizone in 1000 ml of chloroform.\textsuperscript{[12]}

“METHOD U.S.P”

PRINCIPLE
B.P adopts another method of lead poisoning which is based on the brownish colouration produced by the colloidal lead sulphide upon a sodium sulphide with solution under test. If lead content is more than black precipitate of lead sulphide is obtained. the colour produced in test solution is matched against the standard from known amount of lead in nessler cylinder.

METHOD
Two solution of the substance under test are prepared with hot water and acetic acid. One is the primary solution containing a definite but greater amount of substance and placed in one 50 ml nessler cylinder. the other is the auxillary solution containing known amount of test substance in another 50ml nessler cylinder. To this solution a definite amount of of dilute solution of lead nitrate is added. Ammonia and potassium cyanide solution are added to both the solution in nessler cylinder. if solution appear turbid then filter the solution and volume made upto 50ml. both solution are treated with sodium sulphide solution and colour developed. If the colour in the auxillary solution is darken then in the primary the substance contain lead within limits.

The object of using primary and auxillary solution is to compare under identical condition. interference by any unknown entity present in the solution is eliminated by this test.\textsuperscript{[13]}

TREATMENT OF LEAD POISONING
Chelation Therapy Once lead has entered the body, especially bone, it is very difficult to remove.

Accordingly, prevention is the mainstay of treatment. However, chelation therapy may be used to decrease the blood lead concentrations acutely. The final component of treatment is
Chelation therapy. Chelating agents bind metals at two or more sites. Ideally, the chelated metal would be excreted; however, the lead: chelate complex may persist in tissues where the binding occurred or be redistributed to other tissues. An optimal chelating drug should increase lead excretion, be administered easily, and be affordable and safe. Lead removal should halt further toxicity and reverse previous effects.

Several chelating agents are effective in lead excretion, but the chelator of choice depends on the blood lead concentration, the patient’s symptoms and the environmental lead burden. Symptomatic patients should be hospitalized and chelation therapy with Edetate Calcium Disodium (CaNa2EDTA). CaNa2EDTA is an intravenous formulation that has been shown to be effective with British Anti Lewisite (BAL, Dimercaprol) for removal of lead in patients with encephalopathy. Edetate calcium disodium, used alone, may aggravate symptoms in patients with very high blood lead levels. When clinical symptoms consistent with lead poisoning or when blood lead levels are greater than 70 micrograms/deciliter, it is recommended that edetate calcium disodium be used in conjunction with dimercaprol. British-Anti-Lewisite (BAL) or dimercaprol is a small molecule drug which will cross into cells and may prevent the worsening of clinical and biochemical status on the first day of EDTA therapy. Oral chelating agents are available for treatment of lead poisoned patients who have elevated blood lead concentrations and asymptomatic. In the Unites States, 2,3 Dimercaptosuccinic Acid (DMSA, Succimer) is the drug most commonly used. Other oral agents that may be used are DMPS (Unithiol) and penicillamine.[14]

Although the majority of published cases of lead poisoning come from occupational exposures, some traditional remedies may also contain toxic amounts of lead. Ayurveda is a system of traditional medicine that is native to India and is used in many parts of world as an alternative to standard treatment regimens. Here, we report the case of a 58-year-old woman who presented with abdominal pain, anemia, liver function abnormalities, and an elevated blood lead level. The patient was found to have been taking the Ayurvedic medicine Jambrulin prior to presentation. Chemical analysis of the medication showed high levels of lead. Following treatment with an oral chelating agent, the patient’s symptoms resolved and laboratory abnormalities normalized. This case highlights the need for increased awareness that some Ayurvedic medicines may contain potentially harmful levels of heavy metals and people who use them are at risk of developing associated toxicities.[15]
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