SUMMARY

- The toxic impact of certain substances falling under occupational exposure needs to be evaluated to gain knowledge of their health hazards. This will enable monitoring of the risk posed by these toxic substances.

- Lead is a ubiquitous environmental toxin that induces a broad range of physiological, biochemical and behavioral dysfunctions.

- Brain is the main target of lead, as it crosses the blood brain barrier with ease, and causes changes in the metabolism and function of the cell.

- The present study was aimed at investigating the therapeutic efficacy of DL α-lipoic acid, dimercaptosuccinic acid and their combined treatment against lead induced neurotoxicity.

- Lead acetate was dissolved in drinking water and was given to the animals for five weeks to induce toxicity.

- Lead was accumulated in large amount in the hippocampus and blood. Lipoic acid, DMSA and their combined treatment reduced its levels in the blood and tissue.

- Membrane bound enzymes, which play an important role in the maintenance of cell integrity, were inhibited by lead in all brain regions and blood.

- Inhibition of glycolytic enzymes comprises the major toxic effect of lead in the neural tissues.

- There was an accumulation of the heme intermediate, δ-aminolevulinic acid (ALA), a main cause for the production for reactive oxygen species, in the brain and blood of this heavy metal exposed rats. This was due to the inhibition of ALA-D by lead.
High level of lipid peroxidation and decrease in antioxidant status were observed in lead toxicity.

Drug metabolizing enzymes were decreased on lead exposure in the brain as well as in the liver.

Biogenic amines were decreased in the brain regions with concomitant increase of 5-HIAA, a degradative metabolite of serotonin in the lead administered rats.

Programmed cell death or apoptosis was seen in lead administered rats, as evidenced by the high level of DNA fragmentation and increased expression of TNF-α in the blood and brain regions.

The main reasons for cell death are the production of ROS by lead associated with its calcium mimicking action.

Reduction of oxidative stress and chelation of lead by lipoic acid and succimer effectively minimizes the toxic manifestations of lead.

Combined treatment proved to have a better effect than individual treatments highlighting the efficacy of a potent antioxidant and a chelator in combination.
Schematic representation of mechanism of action of lead

**Pb**<sup>2+</sup> → Excreted in Urine

- Inhibition of membrane ATPases
- Enhanced autodissociation of hemoglobin
- ALA accumulation
- ALA-oxyHb coupled autodissociation
- ALA autodissociation
- 4,5-dioxovaleric acid
- ROS

**LIPIDS**
- Lipid oxidation

**PROTEINS**
- Amino acid/protein oxidation

**DNA**
- Oxidised nucleic acids
- Membrane damage
- Alteration of Function

**CELL DEATH**

Lipoic acid prevents ALA accumulation thereby reducing ROS production and also prevents oxidation of macromolecules (lipids, proteins, DNA) by increasing antioxidant status.

DMSA mainly chelates lead from the body and thereby minimizing its toxicity.