

# THE THERAPEUTIC ROLE OF CHELATION IN POISON

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## Abstract

Chelation refers to the coordination to the metal ion with a polydentate ligand. The complex so formed may result in precipitation of the metal or formation of stable, soluble compounds[1]. Trace quantity of several metals are essential constituents of the human body, because activity of many enzymes depends on these chelations. Though the amount of metal present is approx. 3% of body weight, but excess of any metal is harmful to body, its industrial and technological advances, metal pollution of the atmosphere has been increasing fast. Excess concentration of trace metal gradually accumulates in the body, leading to metal induced toxicity. Controlled removal of undesirable metal ions can be achieved by use of appropriate chelating agent[2,3]

Keywords: Chelation, Poisoning, Hydrophilic and Lipophilic

## Introduction

An ideal chelating agent should satisfy all the coordination position of the metal ion with an enzyme or protein. The citing drugs of low toxicity and should not get metabolized, to persist their scavenging function, may be administered orally as well as parentally[4].

Free chelates as drugs [5,6]. some citing drugs are used as antidote for metal poisoning. In controlled dosing antidote circulates in the blood stream, forming complexes with heavy metals, and rapidly excreted in urine.

Dimercaprol [7] or BAL (British Antilewisite) Fig. 1, when injected intramuscularly binds heavy metal ions such as Arsenic, Mercury, Antimony and Gold.

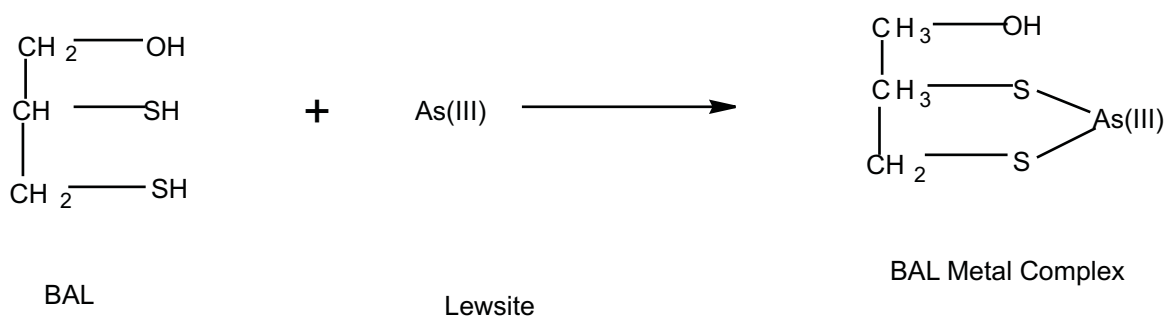


FIG. 1

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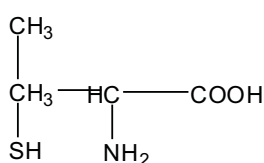
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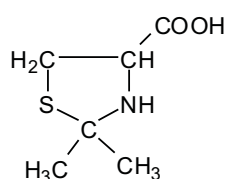
The toxic metals are thus displaced from the tissues, where they bind the -SH groups of various enzymes and interfere with normal enzyme activity. The BAL- Metal complex is excreted rapidly; Dimercaprol injection I.P. is a sterile injection of dimercaprol in a mixture of Benzyl benzoate and Arachis oil, containing 90-100 mg/ml.

D-Penicillamine (fig. 2) is the most effective chelating drug for treatment of Wilson's disease. Acetyl d-Penicillamic (fig. 3) is less toxic and weaker chelating agent than d-penicillamine. Both of these are bidentate chelating agents from soluble complexes with excess copper present in the body, facilitating its renal clearance.



d-penicillamine

FIG. 2



Acetyl d-penicillamine

FIG. 3

Trientine (Triethyl tetramine) orally is claimed to be as effective as d-penicillamine

Desferrioxamine (fig 4) is used for removal of excess iron in the body cysteamine (fig 5) prevents radiation injury, perhaps its ability to sequester with iron & copper ion, released from the cell by irradiation . Dithrocarb has been found useful in the treatment of nickel carboxyl poisoning, also to some extent in acute thallium poisoning and in Wilson's disease.

Sodium Salicylate may be used in layer doses in beryllium poisoning. Aurintricarboxylic acid (Fig. 6) forms insoluble beryllium complexes in the body.

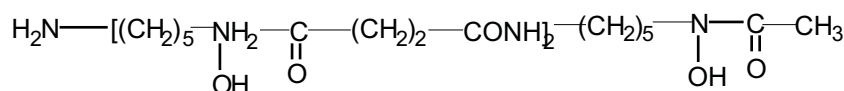


FIG. 4

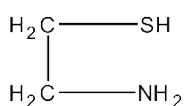


FIG. 5

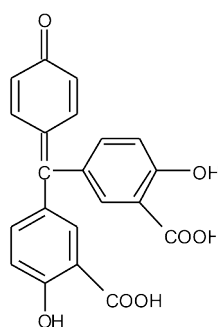


FIG. 6

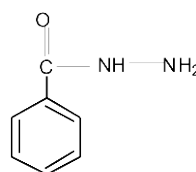


FIG. 7

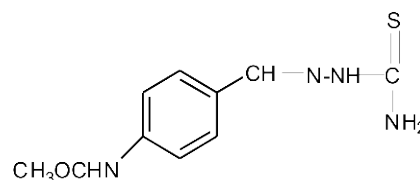


FIG. 8

Tetracycline's and its derivatives are strong chelating agents, inhibit Protein synthesis in bacterial ribosomes. Since magnesium is abundant in ribosomes, the chelating action of tetracycline's is partly by anchoring magnesium ion.

With is nicotinic acid hydrazine (Isoniazide potent anti tubercular) (fig 7) intracellular or extracellular chelation of divalent cations, essential for bacterial metabolism is possible mechanism.

Thiacetazone (P-Acetamido- benzaldehyde thio-semicarbazone) (fig 8) acts by chelation in treating Isoniazide resistant tuberculosis and leprosy.

### Metal chetales as Drugs [8,9,10,11]

Ethylene diamine tetracetic acid (EDTA) can remove metal ions from circulatory system. Free EDTA is toxic; hence monocalcium disodium ethylene diamine tetra acetate (Fig 9) is used intravenously. These salt of EDTA from stable and water soluble complexes with many divalent and trivalent metallic ions and have their therapeutic application to this chelating property. The Ca-Na salt has a high affinity for lead, while the disodium salt exhibits a high affinity for calcium. It is also used in Zinc and Strontium poisoning.

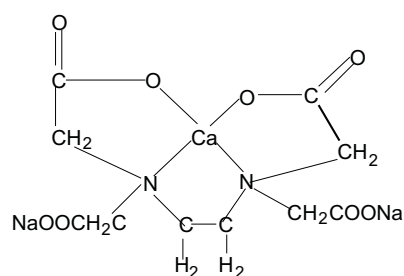


FIG. 9

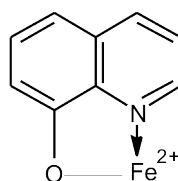


FIG. 10

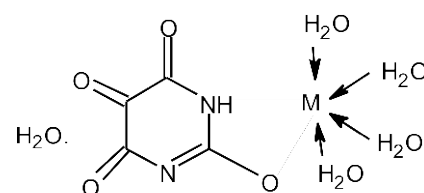


FIG. 11

Now a day's Fe (II) –EDTA chelate (Fig 10) is used as an antianaemic drug. CaH<sub>2</sub>-EDTA is used in renal calculi.

8-hydroxyquinoline (oxine)<sup>3</sup> can complex with iron (Fig 10) normally present in the host and carry it across the cell membranes of bacteria and fungi. The complex is thus capable of bacteria and fungi. The complex is thus capable of acting as an antibacterial spectrum similar to that of penicillin. It is used in lotion for myotic condition of skin, in baby oils etc. A mixture of used 5-Choloro and 5 dicholoro oxine in ointment is used for infection of mouth and throat. 5-chloro-7- iodo oxine (Chinoform) is used for various skin infection. Complexes of gold have been used in the treatment of rheumatoid arthritis.

Metal chelates of p-aminosalicylic acid (PASA) probably executes its antitubercular action by combining with Alloxan (fig 11) exerts its diabetogenic action by combining with the -SH groups of essential enzymes and it may be that the chelates of essential enzymes and it may be that the chelate of alloxan bind to the -SH groups through the metal ion to stabilize the linkage.

### Metal Chelates and Malignancy [12,13,14]

A considerable number of metal complex compounds are known to possess antitumor activity. It is assumed that they deactivate either the carcinogenic metals or all enzymes necessary for rapid growth of both healthy & malignant cells.

Rosenberg[13] reviewed a series of platinum complexes having antitumor activity. He noted that (i) only neutral complexes are active, (ii) only cis-form has medicinal activity. The most widely used complex in chemotherapy is cis-dichloro diamine platinum (II). Some rhodium and iridium complexes, analogues of the active platinum complexes, show antitumor activity.

The role of tungstosilicic acid (TSA), as anti-viral and antitumor agent is well established. From the data available on anti cancer activity of metal complexes, it may be concluded that metal used in these complexes should belong to VIII group of the periodic table, like palladium, platinum, ruthenium and rhodium. Chelating agents should be lipophilic and must closely resemble a nutrient for its easy entrance in a malignant cell across the cell membrane. The metal complex should be in cis-form and it should be sufficiently kinetically stable, so that it remains unchanged during circulation through body fluid.

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