eISSN: 2231-0541 CAS CODEN: PHARN8 An ELSEVIER Covered Journal

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 4 | Issue 6 | November-December 2013 | Pages 1458-1463

Review Article

CHELATION THERAPY

[a]G.K.SUDHAKAR*,[b]VENKATESH KAMATH B,[c]ARAVIND PAI,[d]VASUDEV PAI

[a,c]Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal

[b]Department of Pharmaceutical Biotechnology, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal

[d]Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal

Author for Correspondence: gk.sudhakar@manipal.edu

Received: 23-09-2013 Revised: 11-10-2013

Accepted: 19-10-2013 Available online: 01-11-2013

ABSTRACT

Chelating agents are drugs that complex with and thereby 'hold' metal ions in inactive form that are suitable for mobilization and subsequent excretion. The principal therapeutic use of chelating agent is to treat heavy metal poisoning. This article describes a list of six chelating agents commonly employed in clinical practice.

Key words: Chelating agents, Lead poisoning, Wilson's disease, Iron poisoning, Thalassemia.

INTRODUCTION

Heavy metals are of interest from toxicological point of view. The large scale industrialization and mining have caused occupational diseases due to heavy metals. Metallic contamination of food and water may lead to poisoning. Many herbo mineral available over the counter (OTC) may contribute to heavy metal toxicity[1].

Heavy metals are not metabolized in the body. These cause toxic manifestations, that is, cell function is impaired by combining with one or more ligands {eg. Hydroxyl (-OH), sulphydryl (-SH)}, of the enzymes which are essential for normal physiological functions.

CHELATING AGENTS

Chelating agents are metal binding antidotal chemicals which bind to the ions of heavy metals by forming ionic bond or co-ordinate bond with them. The chemical complex thus formed is called Chelate. It is stable, non-toxic and excreted through kidneys. This process of complex formation is known as chelation. The term is derived from Greek word "Chele" which means claw. The chelating agents are also branded as heavy metal antagonists[2].

An ideal chelating agent should have the following properties

- High solubility in water
- Resistance to biotransformation
- Should be able to reach sites of metal storage
- Should retain activity at body pH
- Rapid excretion of chelate from the body
- Should form non-toxic complex in body

The major disadvantage is that none of the chelating agents are entirely specific for a given metallic ion and are capable of removing important ion like calcium and enzyme cofactors. The chelating agents have flexible molecules with two or more electronegative groups. Accordingly they are classified as bidentate (Dimercaprol, Penicillamine) or polydentate (Disodium edetate, Calcium Disodium edentate, Desferrioxamine, Trientine).

Chelating agents useful as drugs are Dimercaprol,Penicillamine, EDTA and derivatives, Desferrioxamine, Deferiprone, Trientine.

Dimercaprol {BAL (British Anti Lewisite)}

Dimercaprol was developed during world war II in Great Britain, which was synthesized during systematic study of possible antidotes against arsenic vesicant containing war gases like Lewisite (hence the name BAL). Chemically it is dithiol having two sulphydryl groups (-SH).

Therapeutic uses of Dimercaprol

- In acute poisoning due to Mercury, Gold Antimony Bismuth and Thallium.
- As an adjuvant to Penicillamine in copper poisoning and in Wilson's disease.
- As an adjuvant to calcium sodium edetate in lead poisoning.

(Dimercaprol) **(Metal)** **Dimercaprol Metal Complex**

It is contraindicated in Iron and Cadmium poisoning because Dimercaprol-Iron and Dimercaprol-Cadmium complex is itself toxic and causes fever, hypertension, tachycardia, nausea, vomiting and abdominal pain. Hemolytic anemia may occur in patients who are deficient in G-6 PD enzyme.

Penicillamine

Penicillamine is dimethyl cysteine, obtained as degradation product by alkaline hydrolysis of Benzyl Penicillin. It has been found to have strong copper chelating property. It was used in 1956 for Wilson's disease[3]. It selectively chelates copper, lead, zinc and arsenic[4]. The D-isomer is used therapeutically because L-isomer and the racemate produce optic neuritis and are more toxic. The structure of Penicillamine is given below.

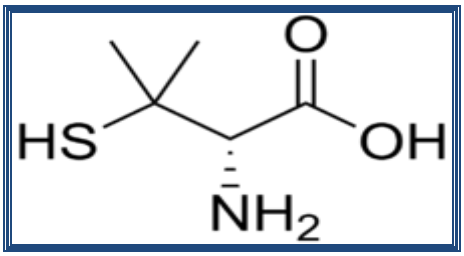


Fig.1.Structure of Penicillamine

Uses of Penicillamine

1. In Wilson's disease (Hepatolenticular degeneration)
   Due to genetic deficiency of ceruloplasmin, a protein which normally binds and disposes off copper from the body. In its absence, plasma concentration of free copper is high and gets deposited in liver, basal ganglia of brain. This causes local degeneration (Extra Pyramidal Neurological Damage).

2. In copper/Mercury poisoning[5].
3. Chronic lead poisoning- May be used as an adjuvant to calcium disodium edentate.
4. Cystinuria and cystine stones- Promotes the excretion of cysteine and prevents its precipitation in the Urinary tract, because Penicillamine-Cysteine complex is more soluble than dicysteine.

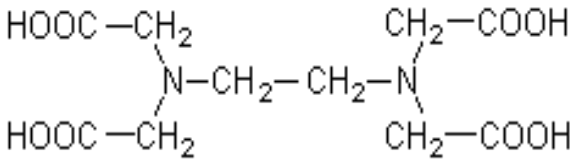
EDTA and derivatives

Ethylene diaminetetraacetic acid (EDTA) is a powerful chelating agent. Its affinity for metallic ions increases in the following order (Ca, Mn, Fe, Co, Zn, Cu, Ni, Cd and Pb). It has been estimated that its affinity for lead is 10^7 times that of calcium. It is insoluble in water, thus not used therapeutically.

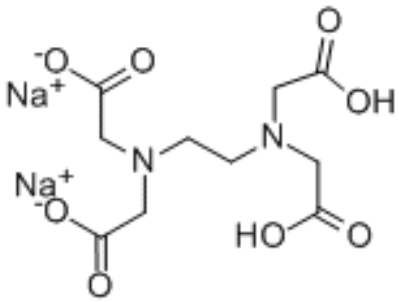
Disodium edetate is dangerous when injected intravenously, since it chelates calcium and may lead to hypocalcaemictetany. Its main use is in topical treatment of lime burns in the eye. Calcium disodium edetate is used to treat lead poisoning[6] (Plumbism). The chelate formed is stable, water soluble and readily excreted by kidneys. This does not produce negative calcium balance (Hypocalcaemia).

Absorption of Calcium disodium edetate after oral administration is poor. It is given by intravenous or intramuscular route[7]. Plasma half-life is 60 minutes. It is not metabolized in the body and does not enter body cells or cerebrospinal fluid and is eliminated through kidney. Side effects include thrombophlebitis, hypotension, lacrimation, muscle pain, sneezing and chills. Renal damage and transient bone marrow depression may occur.

The structure of EDTA, Disodium edetate and Calcium disodium edetate are given below:



Structure of EDTA



Structure of Disodium EDTA

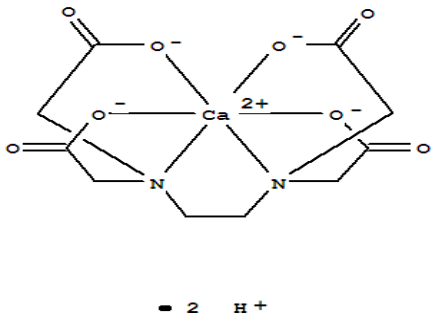


Fig.2. Structure of calcium EDTA complex

Desferrioxamine

Desferrioxaminemesylate, obtained from *Streptomyces pilosus*, is a potent and specific chelator of Iron. It readily binds to ferric iron to form Ferrioxamine, a stable and water soluble chelate. It removes loosely bound Iron from Haemosiderin and Ferritin, but not from Haemoglobin or Cytochrome. Another desirable property is its low affinity for calcium.

Uses of Desferrioxamine

1. In Iron poisoning especially in children.
2. In transfusion siderosis which occurs in Thalassemia patients who receive repeated blood transfusion.

Deferiprone

This is an orally effective, Iron chelator, less effective than Desferrioxamine.

Uses of Deferiprone

1. In acute Iron poisoning.
2. In Iron overload during liver cirrhosis.

Trientine

Trientine (Triethylenetetramine) is an effective as Penicillamine in reversing the neurological lesions of Wilson's disease[8].

Various chelating agents for Heavy metal poisoning with respect to usual regimen is given in (Table 1).

Table.1.Chelating agents for Heavy metal Poisoning[9]

Chelating agent	Antidote for poisoning	Route of administration	Mode of administration
Dimercaprol	Arsenic, Mercury, Gold	Intramuscular	2.5 mg/Kg at 4-6 hr interval for first two days, then reduced to two injections/day for a total of ten days
Penicillamine	Copper, Lead, Iron, Mercury	Orally	250 mg four times a day
Calcium Disodium Edetate	Lead	Intravenous	One gm in 250 to 500 mL of 5% dextrose solution by *i.v* drip over 1 hr twice daily for 5 days
Desferrioxamine	Iron	Intravenous	400-600 mg once or twice daily and in acute poisoning 8-12 gm by gastric tube plus 2 gmi.v or i.m
Trientine	Copper	Orally	750-1250 mg/day in two to four divided doses on an empty stomach

REFERENCES

1. Satoskar RS, Bhandarkar SD, Rege NN. Pharmacology and Pharmacotherapeutics. 20th ed. Mumbai, India: Popular Prakashan Pvt. Ltd; 2007. p. 1040.
2. Aposhian HV, Aposhian MV. MESO-2,3-dimercaptosuccinic acid: Chemical, Pharmacological and toxicological properties of orally effective metal chelating agents. *Annual Review of Pharmacology and Toxicology* (1990);30: 279-306.
3. Netter P, Banwarth B, Pere P, Nicholas A. Clinical pharmacokinetics of D-Penicillamine. *Clinical Pharmacokinetics*. (1987); 13(5): 317-333.
4. Peterson RG, Rumack BH. D-Penicillamine therapy of acute arsenic poisoning. *The Journal of Paediatrics*. (1977); 91(4):661-666.
5. Snodgrass W et al. Mercury poisoning from gold ore processing. *JAMA*. (1981); 246(17):1929-31.
6. Nadig RJ.Treatment of *lead poisoning*. *JAMA*.(1990);263(16):2181-2182.
7. *Cory-Slechta DA, Weiss B. Efficacy of the chelating agent*CaEDTA in reversing lead-inducedchanges in behavior.*Neurotoxicology. 1989;* 10(4):685-97.
8. Walshe JM. Treatment of wilson's disease with trientine (triethylenetetramine) dihydrochloride. *The Lancet*. (1982);319(8273): 643-647.
9. Satoskar RS, Bhandarkar SD, Rege NN. Pharmacology and Pharmacotherapeutics. 20th ed. Mumbai, India: Popular Prakashan Pvt. Ltd; 2007. p. 1045.