Topic: Complexing and Chelating Agents Used in Therapy, Poisons and Antidotes

Subject: General Chemistry

Class: F.Y. B. Pharm. (Sem.- I)

Academic Year: 2018-19

Programme: 2018-2022

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Mapping of TLO with Course outcomes (Cos)

Sr. No.	Topic Learning Outcomes	COs	BL
1	Define Complexing agents and memorize various chelating agents.	CO4	L2
2	Explain Chelating agents, poisons and antidots.	CO4	L2
3	Identify and memorize chelating agents, antidots used for therapy.	CO4	L2

Introduction

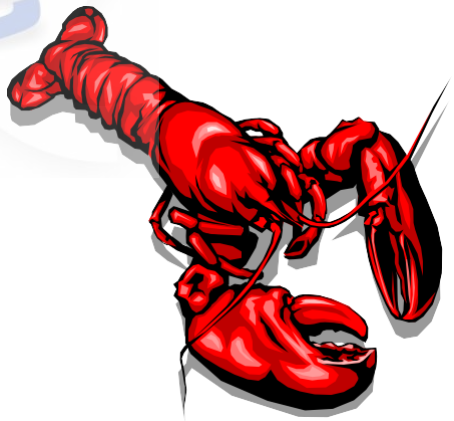
- 80 metals in periodic table.
- Metals causing poisons are lead, mercury, arsenic, cadmium etc.
- Act as a protoplasmic poison by inhibiting essential enzymes.
- Exert toxic effects by combining with and inactivating functional groups of enzyme like SH, COOH, NH_2, OH.

Chelating agents

Chelating agents: Agents having ability to form complexes with heavy metal and prevent the binding of metallic ions to ligands of the body.

Chele =crab's claw

Ligare =to bind



Chelating agents

- Have two or more electronegative groups that form stable coordinate covalent bonds with the cationic metal atom.
- **Chelator–metal complex** is stable, biologically inert and excreted in urine.
- Thus appropriate chelating agent can be effectively used in cases of **heavy metal poisoning**.

Mechanism Of Action

Drug + Metallic ions

↓

Non toxic , water soluble complex

↓

eliminated by the kidney

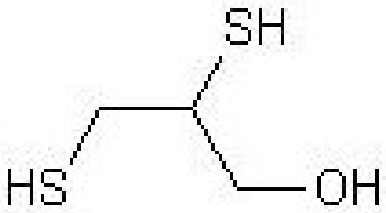
Ideal Chelating Agents

- More affinity for metals than endogenous ligand.
- High solubility in water.
- Resistance to biotransformation.
- Form non toxic complexes with toxic metal.
- Accelerate mobilization and/or removal of the metals.
- Cheap and easy to administer.
- Easy excretion of chelating complex.

Useful chelating agents

Chelating agents useful as drugs are:

- Dimercaprol (BAL)
- Disodium edetate
- Calcium disodium edetate
- Pencillamine
- Desferrioxamine



Dimercaprol (BAL)

- BAL: British Anti-lewisite.
- It was synthesized during the world war II by Britishers as an antidote to arsenic gas.
- Oily, pungent smelling, viscous liquid.
- It is administered i.m in oil (arachis oil).
- -SH ligands of dimercaprol compete with –SH groups of enzymes for heavy metal.
- Dimercaprol –metal complex is stable and excreted in urine.

Dimercaprol *Cont...*

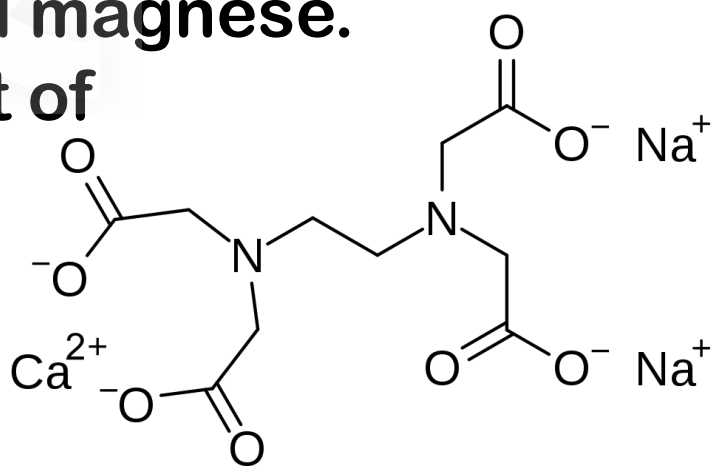
Uses:

- For the treatment of **arsenic and mercury poisoning**
- As adjuvant to Cal. disod. Edetate in lead poisoning.
- As an adjuvant to pencillamine in copper poisoning and in Wilson's disease (Degeneration of brain and liver tissue due to increased level of copper).

Dose: 2-3mg/kg 4hr/2days

Calcium disodium edetate (Ca Na_2 EDTA)

- Calcium complex of the disodium salt of ethylenediaminetetraacetic acid (EDTA).
- White crystalline granules or White crystalline powder.
- Odorless, slightly hygroscopic, and faint saline taste.
- Soluble in water and stable in air.
- It is primarily used for treatment of lead poisoning.
- It is also used in poisoning due to copper, nickel, Cadmium, Zinc, Chromium, and magnese.
- It has no value for the treatment of Mercury, arsenic & gold.



Calcium disodium edetate ($Ca\ Na_2$ EDTA) *Cont...*

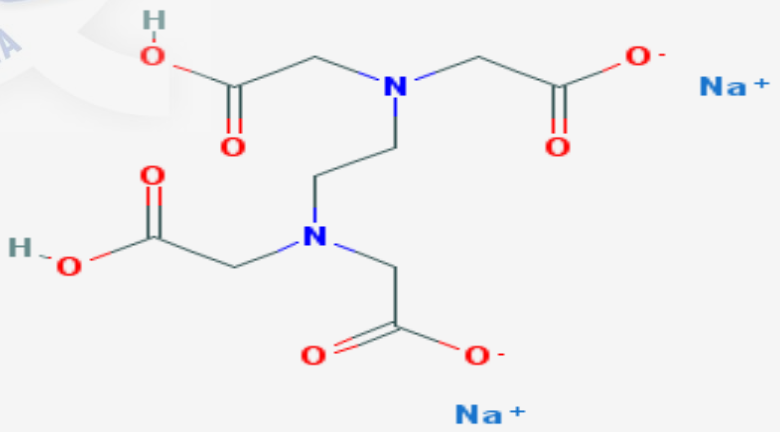
- EDTA preparations have strong affinity for calcium, therefore disodium calcium form is used to avoid hypocalcemic states.
- Removes lead from the tissue by forming an inactive soluble complex which can be removed by the kidneys and excreted in urine.

Dose:

- Intravenous infusion: 75 mg/kg of body weight, administered in 250 or 500 ml of isotonic sodium chloride solution.
- Intramuscular injection: 75mg/kg as 20% solution in 0.5% to 1.5% procaine.

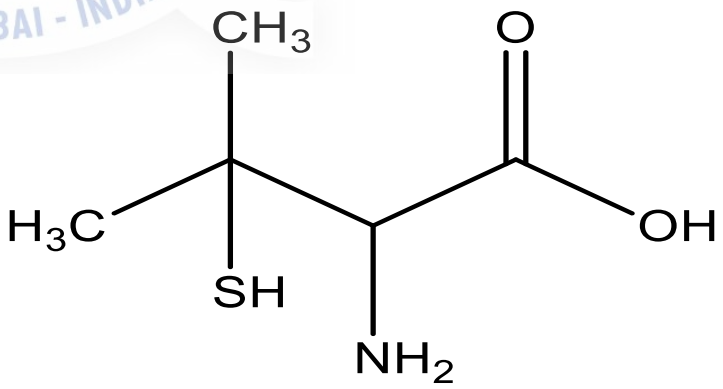
Disodium edetate (Na_2 EDTA)

- White crystalline powder, soluble in water.
- Chelate same metals as the disodium calcium EDTA.
- High affinity for calcium, so chance of hypocalcemia during therapy.
- Can be used for emergency control of hypercalcaemia.
- Useful in treatment of cardiac arrhythmia when associated with high blood level of calcium.
- Dose: 50mg/kg i.v.
  over 2- 4hours



Penicillamine (Dimethylcysteine)

- White or off white crystalline powder.
- Water soluble and slightly soluble in alcohol.
- Degradation product of penicillin.
- Capable of forming soluble complexes with copper, iron, mercury, lead, gold, and other metals.
- It has strong ***copper*** chelating property and used for treatment of Wilson's disease (inability to regulate copper balance, with the consequence that toxic amount of copper are deposited in tissues like eye, liver, brain, and kidney).



Penicillamine *Cont...*

- Another use of penicillamine is the treatment of gold dermatitis.
- It is also used in the treatment of Cystinuria (the presence of amino acid cystine in the urine). This treatment is not related to metal chelating abilities..
- Unlike other chelating agents, the usual route of administration for penicillamine is oral.
- Dose: Oral dose is 250 mg four times a day.

Deferoxamine Mesylate

- White crystalline powder.
- Soluble in water and aqueous solution is stable at room temperature for two weeks.
- It is naturally produces by *Sterptomyces pilosus* as ferric complex. After chemical removal of iron, the chelating agent is obtained methylsulfonate salt.
- It has affinity for ferric ion with which it forms stable, water soluble complex.
- It is used for the treatment of acute iron toxicity.
- **Dose:**

I.M. or I.V. Dose of 1gm initially, then followed by 500mg every 4-12 hour.

Antidotes

An antidote is an agent that counteracts a poison.

Mechanism of antidotes by one of three ways:

1) By counteracting the effects of a poison by producing other effects (physiological antidote)

e.g.: Sodium nitrite converts hemoglobin into methemoglobin in order to bind cyanide.

2) By changing the chemical nature of the poison (a chemical antidote)

e.g.: Sodium thiosulphate causes conversion of cyanide to non toxic thiocyanate.

3) By preventing the absorption of the poison into the body (a mechanical antidote)

e.g.: Activated charcoal which adsorbs poison prior to absorption. Copper sulphate forms insoluble precipitate with poison like phosphorus.

Cyanide Poisoning

- Cyanide (CN^-) combines with the ferric ion (Fe^{+3}).

- Cyanide poisons by combining with ferric ion of cytochrome oxidase which stops electron transfer and thereby stops cellular respiration.

- Cyanide poisoning is treated by combination of sodium nitrite and sodium thiosulfate.

- **Sodium nitrite causes oxidation of ferrous ion (Fe^{+2}) of hemeglobin to the ferric ion (methemoglobin) which then combines with cyanide that has not yet entered the cell.**

$$NaNO_2 + \text{Hemoglobin} \longrightarrow \text{Methemoglobin}$$

$$HCN + \text{Methemoglobin} \longrightarrow \text{Cyanomethemoglobin}$$

- **Following the injection of Sodium nitrite, I.V. Infusion of sodium thiosulfate is given.**
- **Thiosulfate ion catalysed by enzyme rhodanese, reacts with cyanide to form the relatively nontoxic thiocynate ion which is excreted in the urine.**

$$Na_2S_2O_3 + CN^- \xrightarrow{\text{rhodanese}} SCN^- + Na_2SO_3$$

Sodium nitrite ($NaNO_2$); MW: 69.0

➢**Sodium nitrite** is the inorganic compound with the chemical formula $NaNO_2$.

➢ It is a white to slightly yellowish crystalline powder that is very soluble in water and is hygroscopic.

➢Mild saline in test.

➢ It is a useful precursor to a variety of organic compounds, such as pharmaceuticals, dyes, and pesticides.

Uses: Antidote for cyanide poisoning & also as antioxidant.

➢Also used in meat packing as it helps maintain the desired red color and restricts the growth of *Clostridium botulinum* spores.

Dose: I.V. 10 to 15 ml of a 3% solution for treating the cyanide poisoning.

Sodium Thiosulfate ($Na_2S_2O_3.5H_2O$) Mol. Wt.: 248.18

- Large, colorless crystals or crystalline powder.
- Hygroscopic in nature.
- Aqueous solution is neutral or slightly alkaline to litmus.
- Very soluble in water and insoluble in alcohol.

Use: as an antidote for cyanide poisoning.

Dose: I.V. 1 gm in 5 to 10% solution.

Adsorbents

- Adsorbents are used to remove the toxic substance before it can be absorbed into the body.
- **Activated charcoal** is used to treat emergency poisoning before emesis.
- It occurs as a fine, black, odorless, tasteless powder, free from gritty matter.
- Activated charcoal is recommended as a component of first aid kits.

Activated charcoal

- A mixture of two parts activated charcoal, one part magnesium oxide and one part tannic acid is known as universal antidote. This mixture is considered as inferior to the use of activated charcoal alone.
- Compounds effectively bound by activated charcoal in in vivo experiments include paracetamol, aspirin, amphetamine, chloroquine, chlorpheniramine, kerosine, mercuric chloride etc.
- Activated charcoal in a charcoal-to-poison ratio of 5:1 to 10:1 is usually administered as pure powder dispersed in water.
- Once the poison passes out of the stomach, emesis and gastric lavage are of little benefit, and activated charcoal may be useful as it can catch up the poison in the intestinal tract.

Precipitants

- Inorganic salts used as antidotes because they forms insoluble precipitates with cations of heavy metals.
- This prevents absorption, since the cations must be in solution in order to be systemically absorbed.
- After precipitating the heavy metals, the gastric contents are removed by lavage or inducing emesis.

E.g.: Copper sulphate is used for treatment of phophorus poisoning.

$$2P + 6CuSO_4 + 8H_2O \longrightarrow Cu(H_2PO_4)_2 + 5Cu + 6H_2SO_4$$

Copper sulphate is used for both topical and gastric exposure to phosphorus.

Copper sulphate (Cupric sulphate, Blue vitriol)

- It is blue colored crystalline granules or powder.
- Nauseous and metallic taste.
- Freely soluble in water and in glycerine
- Molecular formula: $CuSO_4.5H_2O$
- Molecular weight: 249.7

Uses: As antidote for phosphorus.

- As an **emetic**
- As an **astringent** and also as a **fungicide**
- It is an ingredient of **Benedict's reagent** and **Fehling's reagent**.

Magnesium Sulphate ($MgSO_4.7H_2O$); MW.: 246

- Colorless crystals usually needle-like.
- Cooling, saline bitter taste.
- Hygroscopic and solution is neutral to litmus paper.
- Freely soluble in boiling water and little soluble in alcohol.

Uses:

- Used in barium poisoning to form insoluble barium sulfate and in lead poisoning to form insoluble lead sulphate.
- Cathartic
- Anticonvulsant

Sodium Phosphate ($Na_2HPO_4.7H_2O$) MW.: 268

- Colorless granular salt.
- Hygroscopic in nature.
- It is freely soluble in water.

Uses:

- Treatment of iron poisoning through formation of the insoluble iron phosphate salt.
- Cathartic

References

- Inorganic medicinal and pharmaceutical chemistry, J.H. Block, E.B. Roche, T.O. Soine and C.O. Wilson. Lea & Febiger, Philadelphia, PA, 1986, Page no.: 39-46.
- Inorganic medicinal and pharmaceutical chemistry, J.H. Block, E.B. Roche, T.O. Soine and C.O. Wilson. Lea & Febiger, Philadelphia, PA, 1986, Page no.: 430-435.

Review questions to ensure attainment of TLOs/ COs

Sr. No.	Review questions	COs with Bloom's Level
1	Write a note on cyanide poisoning and its treatment.	CO4 (L2)
2	Classify the antidotes with suitable examples. Give its significance in cyanide poisoning.	CO4 (L2)
3	Explain chelating/complexing agents.	CO4 (L2)
4	Define Complexing agents and enlist various chelating agents used in therapy.	CO4 (L2)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Thank You