# Inorganic Pharmaceutical Chemistry

## Essential and trace ions

## Lecture three


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## 1) Iron

- **The complement of iron**: There are three postulate explanations that control of the intestinal iron absorption:
    1. Mucosal block hypothesis.
    2. Active transport hypothesis.
    3. Iron-chelate hypothesis.

## 1. Mucosal block hypothesis:

- Iron absorption regulated and controlled by availability of apoferritin.

- The dietary or administered iron is reduced to ferrous form which diffuses into the mucosal cell where it is oxidized and then combined with apoferritin which is being continually formed and destroyed to form stable ferritin ,the iron carrying protein.

- As ferritin it crosses the cell and is released to be reduced again to ferrous iron for diffusion across the serosal cell membrane (membrane covering the intestine) and eventual reoxidation to ferric iron and combination with the iron- transport protein (transferrin).

- In this form it is transferred to the liver for storage or to the bone marrow for use in heme synthesis for erythrocyte production.

- Once the full complement of ferritin is obtain for a cell it can no longer pick up iron.

- Further absorption occur only in cells that do not have their full amount of ferritin or if the ferritin unloads its iron thorough the serosal membrane to regenerate apoferritin.

- Among the numerous points against this hypothesis is the facts that no maximum limit of absorption has been demonstrated, that increased amount (although smaller percentage) of iron are absorbed from large doses, that unphysiologic amounts of iron are required to show the blocking effect, and that nonferritin-bound iron is found in intestinal mucosal cells.

## 2. The active transport hypothesis:

- As in the mucosal block mechanism, $Fe^{+2}$ enters the mucosal cell by diffusion where it combines with endogenous low M.Wt ligands or it stored as ferritin.

- To cross the serosal membrane into the blood a specific transport system intimately linked to ATP has been suggested.

- The control of iron entry into the blood occurs by this active transport system.

- Once past the serosal membrane the events are the same as postulated by the mucosal block hypothesis.

- One of the most telling points against this hypothesis is the fact that iron movement is not affected by an anaerobic condition, where as other known active transport processes (e.g. $Na^{+}$) are vitally affected.

# 3. The iron chelate hypothesis:

- It proposed that primary control is exerted by exogenous or endogenous ligands or chelating agents which can bind either oxidation states of iron to form low M.Wt complexes capable of passively diffusing through the mucosal cell membrane from the intestine.

- Within the cell the iron can be transferred to other endogenous ligands or stored as ferritin.

- The major attributes of this theory are that no redox reactions or metabolic energy requirements are directly involved.

- Points against this hypothesis:

1. There is doubt that low M.Wt chelates are present in the GIT cells.

2. The suggestion that both $Fe^{+2}$ and $Fe^{+3}$ are equally complexed for diffusion into the mucosal cell could be difficult to rationalize, because $Fe^{+2}$ absorption more than $Fe^{+3}$ (due to poor solubility of $Fe^{+3}$ salts as compared to $Fe^{+2}$ salts).

- A person deficient in iron will become anemic, anemia is a general term for conditions in which:

1. Circulating red blood cells are deficient in number.
2. Deficient in total haemoglobin content per unit of blood volume.

- The net result is lower oxygen carrying capacity by the blood.

- Anaemia can be caused by:

1. Excessive loss of blood.
2. Blood destruction.
3. Decreased blood formation.

- Excessive blood loss can be caused by:

a. Bleeding ulcer.
b. Hemorrhaging.
c. Menstrual flow.

- Blood destruction can be caused by:

a. Hemolytic agents (drug therapy, infections, toxins).
b. Defective hemoglobin (sickle cell anemia, thalassemia).

- Decreased blood formation can be caused by:

a. Deficiencies of key materials (cobalamin, folic acid, pyridoxine and iron).
b. Infections.
c. Renal insufficiency.
d. Malignancy.
e. Marrow failure.

- An iron compound used for replacement or supplemental therapy must meet two requirements it must:

1. Be biologically available.
2. Be non irritating.

- Usually water soluble, ferrous sulphate is the standard to which other iron salts are compared.
- Sustained released iron formulation have been utilized as a means of minimizing the irritant properties of iron.

- Parenteral iron preparations are indicated only in those conditions where either:

1) Iron absorption is defective (Steatorrhea, partial gastrectomy).
2) The iron salt may be irritating (ulcerative colitis, peptic ulcer).

## Official iron product

1. Ferrous sulphate $FeSO_4.7H_2O$

- Occur as pale, bluish green crystals or granules which are odorless, has a saline test and is efflorescent in dry air.

- It is oxidizes readily in moist air to brownish yellow basic ferric sulphate.
- Ferrous sulphate is the most widely used oral iron preparation and is considered as the drug of choice for treating uncomplicated iron deficiency anaemia.
- It can be irritating to the GIT mucosa due to the astringent action of soluble iron but it is probably no more irritating than any other iron salt when equivalent doses are used.
- Found as ferrous sulfate tablets, ferrous sulfate syrup, dried ferrous sulfate.

2. Ferrous fumarate.

- It is resistant to oxidation on exposure to air so it may be superior to both ferrous sulphate and gluconate.
- Found as tablets.

3. Ferrous gluconate.

- It has a good bioavailability.
- Found as tablets.

## 4. Iron dextran injection

- It is used only in confirmed cases of sever iron-deficiency anemia where oral therapy is contraindicated or ineffective, or if the patient can not be relied upon to take oral medication.
- Found as intramuscular injection only.

## 5. Iron sorbitex injection

- The patient's urine can become dark on standing due to the formation of iron sulfide.
- Found as intramuscular injection only.

## Nonofficial iron preparations

1. Dextriferron.
2. Ferrocholinate.
3. Ferric ammonium citrate.
4. Green ferric ammonium citrate.
5. Ferric cacodylate.
6. Ferric chloride.
7. Ferric hypophosphite.
8. Soluble ferric phosphate.
9. Ferric pyrophosphate
10. Ferric glycerophosphate.
11. Saccharated ferric oxide.
12. Ferrous carbonate.

## 2) Copper

- It is required for many enzymes, synthesis of haemoglobin and for normal bone formation.
- Unlike iron it is believed that most of the population obtain the sufficient amount of copper from food, water, and cooking utensils.
- Copper supplements are probably not necessary.

- Copper is solubilized in the acidic stomach and is absorbed from the stomach and upper small intestine.

- From intestine copper moves into the blood where it exists first as copper albumin complex, then goes to the liver where the copper become part of copper protein, ceruloplasmin.

- Copper is found in the brain in form of cerebrocuprein, in blood cells as erythrocuprein.

- Several roles in metabolism have been attributed to copper :

1. haemoglobin formation.

- Copper is required to prevent anemic conditions through:

a. Facilitate iron absorption.

b.Stimulates enzymes involve heme and/or globin biosynthesis.

c. Could involve in metabolization of stored iron.

2. It is important in oxidative phosphorylation (ATP production).

3. It is associated with the formation of aortic elastin.

4.It is a component of tyrosinase, an enzyme responsible for conversion of tyrosine to the black pigment, melanin.

- **Wilson disease** a condition of excess copper storage.

- There is a decrease in ceruloplasmin conc. in the blood ,and characterized by presence of large amounts of copper in the brain along with an excessive urinary output, increased copper levels in liver, brain, kidney, and cornea.

- **Pencillamine** is the drug of choice which is a chelating agent, in addition to diet restriction.

- **Uses of copper as copper sulfate in:**

1. Topically as fungicide and astringents.

2. Antidote for phosphorous poisoning.

3. Essential component of Fehling‘s and benedict‘s solutions which are used for determination of reducing sugars (glucose).

- A positive test is the production of cuprous oxide precipitate.

# 3) Zinc

- Zinc essential for:

1. Several enzymes as alcohol dehydrogenase, alkaline phosphatase, carbonicanhydrase, glutamic dehydrogenase & others.
2. Zinc bound to RNA stabilising secondary and tertiary structures.
3. For normal growth and reproduction.
4. It has a beneficial effect on tissue repair and wound healing.
5. Zinc complexes with insulin present in B cells of pancreas.
6. Necessary for vit. A mobilization from liver & vit. A metabolism affected by zinc deficiency.

**Low plasma zinc level is found in:**

1. Alcoholic cirrhosis (progressive liver Disease).
2. Uremia.
3. Myocardial infarction.
4. Down's syndrome (mongolism).
5. Cystic fibrosis with growth retardation.
6. Pregnancy.
7. Women taking oral contraceptive, etc.

- Food sources of zinc includes : fish, nuts, meat, legumes and milk.

- A person on vegetable diet may not receive a sufficient amount of zinc (10-15 mg daily) because phytic acid which found in vegetable proteins such as soybean combine with zinc and decreases its absorption.

# 4) Chromium

- It is an essentialtrace element. It is necessary for optimal growth of experimental animals, in large quantities it is toxic.
- It levels are higher in infants than adults.
- The pharmacodynamics actions of chromium salts, chromate, dichromate are very similar, they are distractive to tissue, regardless of whether applied topically or administered orally.
- When taken internally they produce nephritis and glycosuria.
- Person exposed to chromate dust develop deep ulcers of the skin and nasal mucosa that heal slowly.

# 5) Manganese

- Highest concentration occurring in bone, liver, pituitary, pineal and lactating mammary glands.
- It is used in many metalloproteins, associated with ribonucleic acid (play a role in protein synthesis), oxidative phosphorylation, fatty acid metabolism and cholesterol synthesis.
- Chronic manganism (manganese poisoning): occur due to excessive manganese intake, chest hair will usually contain quite a high level of manganese and scalp hair which normally has no manganese will also contain manganese.
- Manganism is similar to Parkinson's disease. Levodopa has been successful in relieving many symptoms.

## 6) Molybdenum

- It is present in all plant and animal tissues. The largest amounts are found in liver, kidneys, bone and skin. It has been found associated with Flavin-dependent enzymes.
- The only current use of molybdenum today is as the oxide together with ferrous sulfate as a hematinic preparation in the form of tablets, capsules and drops.

## 7) Selenium

- It considered toxic when taken internally.
- As a selenium sulfide suspension used for treatment of seborrheic dermatitis of the scalp (dandruff).
- There have been attempts to replace sulfur with selenium in pharmacologically active and metabolically important compounds, because it is below sulfur in periodic table.

## 8) Sulfur

**Sulphur is widely distributed throughout the body in:**

1. Proteinase as:
    a. Sulfhydryl groups of cysteine.
    b. Disulfide linkages from cystine
2. Mucopolysaccharides and sulfolipids as sulphate salts and esters.

- **Sulfur has been used therapeutically as:**

1. Cathartic action.
2. Parasiticide in scabies.
3. Stimulant in alopecia.
4. Fumigation.
5. Miscellaneous skin diseases.

# 9) Iodine (iodide)

- Iodide is an essential ion necessary for the synthesis of two hormones produced by thyroid gland, triiodothyronine ($T_3$) and thyroxine ($T_4$), (Structures required).

- Internally Iodine or Iodide can be administered, since Iodine is reduced to Iodide in the intestinal tract, for solubility reasons it is more common to administer an iodide salt.

- Iodine have:

1. Biochemical role in thyroid hormone formation.
2. Pharmacological action as:
    a. Fibrolytic agent.
    b. Expectorant .
    c. Bactericidal agent.

- The usual daily Iodine requirement for an average male is 140 micrograms and female about 100 micrograms.

- Lack of sufficient iodine in the diet results in an enlargement of thyroid gland known as simple or colloid goiter.
- When iodine is administered its uptake is governed by three principle factors:

1. The character of local thyroid tissue because abnormal adenomatous (tumorous) thyroid tissue has a slower uptake of iodide and a lower content of iodine than normal tissue.

2. Blood level of inorganic iodide ,because of high level keeps the iodine at high level in the colloids thus using up only a small part ofthe administered iodide.

3. The level of TSH in blood which is hormone secreted pituitary gland which stimulate uptake of iodide by the gland, incorporate iodine into thyroxin and stimulate release thyroid hormones from the gland.

- Excessive amount of iodide inhibit release of TSH and decrease production of thyroid hormones.

**Thyroid gland regulates:**

1. Metabolism of the body.
2. Affect growth and development of the body.

Iodide therapeutically used as improving agent in hyperthyroidism, Fibrolytic agent in leprosy, an expectorant, "alterative" (archaic term for drug that reestablishes the health of the individual).

**Official iodine products:**

1. Iodine, found as (Strong Iodine Solution, Iodine tincture, Iodine solution, Iodine ampules).

2. Potassium Iodide, found as (potassium Iodide solution, Strong Iodine solution).

3. Sodium Iodide, found as (Iodine tincture, Iodine solution, Iodine ampules).