Anti-Anemic Drugs

Hematopoiesis

▪ It is the production of erythrocytes, platelets and leukocytes from stem cells in the bone marrow.

▪ It requires a constant supply of three essential nutrients:

1. Iron

2. Vitamin B12

3. Folic acid

▪ Drugs used to treat anemia are called Hematopoietic Growth Factors

▪ They are proteins that regulate the proliferation and differentiation of hematopoietic cells

Anemia: Deficiency in oxygen- carrying erythrocytes.

Anti-anemic drugs

● They are administered in the case of iron deficiency and other hypochromic anemia, they include:

1. Iron

2. Pyridoxine, riboflavin, copper.

● Drugs administered in the case of megaloblastic anemia:

1. vitamin B12

2. folic acid

3. hematopoietic GFS

● Erythropoietin is given in the case of chronic renal failure

# Agents Used To Treat Anemia

Iron

▪ Iron deficiency is the most common cause of chronic anemia.

▪ Total Body Iron:

○ 4 g in the adult male

○ 2.5 g in the adult female

▪Source: meat & green vegetables.

▪ Iron forms the nucleus of the iron-porphyrin heme ring, which together with globin chains forms Hb.

▪ Hb reversibly binds oxygen (delivery).

▪ Iron deficiency causes small RBCs and insufficient Hb are formed→ mycrocytic hypochromic anemia.

Pharmacokinetics

▪ All of the iron used to support hematopoiesis is reclaimed from catalysis of the Hb in senescent/damaged erythrocytes.

▪ Dietary requirements are small and easily available in food.

Iron absorption:

▪ Iron is actively absorbed in duodenum and proximal jejunum in the ferric form (+++) and is complexed to other organic & inorganic molecule.

▪ The acid in the stomach and hydrolytic enzymes in small intestine release the iron from these complexes.

▪ It is then reduced to the ferrous (++) form (more readily absorbed).

▪ Absorption is increased by: glucose, amino acid and ascorbic acid.

▪ It is decreased by: phosphate, bicarbonate, bile acids, antacids and tetracycline.

▪ Heme iron in meat Hb and myoglobin can be absorbed intact.

▪ Iron in vegetables and grains is tightly bound to organic cpds ; Available for absorption

▪ Excess iron is stored in mucosal cell as ferritin, a water soluble complex.

Distribution:

▪ Iron is transported in the plasma bound to transferrin, a β globulin binds 2 molecules of ferrous iron. The iron is transported to the marrow for use and storage.

▪ The transferrin-iron complex enters maturing erythroid cells by a specific receptor mechanism.

▪ Transferrin concentration is increased if the iron store is depleted and in iron deficiency anemia.

Storage:

▪ When free iron level are high, apoferritin is produce to sequester iron and protect organs from toxic effect of excess free iron.

▪ Iron is stored in intestinal mucosal cells and as ferritin, in macrophages in liver, spleen & bone.

Elimination:

▪ No mechanism for excretion.

▪ Small amounts are shed in the feces and in the bile.

Use of iron:

▪ Treatment of iron deficiency anemia

▪ Prevent anemia in conditions where there is increased iron requirement:

- Premature infants

- Children during rapid growth periods

- Pregnant & lactating women

- Increased blood loss and iron (heavy menstruation)

- Patients with chronic kidney disease and treatment with growth factor erythropoietin (parenteral iron is preferred)

- Malabsorption, inadequate iron absorption, GIT bleeding, gastrectomy and severe small bowel disease

Treatment

▪ Iron deficiency anemia is treated with oral or parenteral iron

▪ Oral iron if GIT is normal

▪ Oral iron: 200–400 mg for 3 – 6 months

▪ Forms: FERROUS sulfate, gluconate, fumarate or succinate

▪ All are effective and inexpensive

Side effects

▪ Nausea, epigastric discomfort, abdominal cramps, constipation or diarrhea with black stools

Treatment: lower the dose or take the tablet immediately after the meal

Parenteral Iron

▪ It is given post-gastrectomy, small bowel section, inflammatory bowel disease, noncompliance of oral iron, malabsorption syndrome, marked blood loss and advanced chronic renal disease

▪ Iron dextran: stable complex of ferric OH and low molecular weight dextran (IM / IV infusion)

▪ Advantage of IV: eliminates local pain and tissue staining (which are side effects of IM) and allow delivery of entire iron dose

▪ Also Iron sorbitol may be given (IM).

Side effects

▪ Headache, light-headness, fever, arthralgia, nausea, vomiting, back pain, flushing, urticaria, bronchospasm

▪ Rare: anaphylactic and death.

▪ Also dextran can cause hypersensitivity reactions

Alternative Preparations

Iron-sucrose complex and iron Na gluconate complex. They are only available as IV, and produce less hypersensitivity than dextran.

# A-Acute Iron Toxicity

Sign and symptoms

▪ Necrotizing gastroenteritis, vomiting, abdominal pain, bloody diarrhea, followed by shock, lethargy and dyspnea and severe metabolic acidosis, coma and death.

Treatment

▪ Whole bowel irrigation or gastric lavage: 1% NaHCO3.

▪ Antidote: Deferoxamine (Desferroxamine), potent iron-chelating agent, it binds absorbed iron and promotes its excretion in urine and feces. (intragastric, IM, SC, IV, infusion).

# B-Chronic Iron Toxicity

▪ Overload or hemochromatosis results when excess iron is deposited in the heart, liver, pancreas and other organs. It can lead to organ failure and death.

Causes:

▪ Patient with inherited hemochromatosis (excessive iron absorption, tissue damage),

▪ Patients who receive many blood transfusions over a long period of time as is the case with chronic hemolytic anemia (thalassemia)

Treatment:

1-Intermittent phlebotomy: removing one unit of blood every week until all excess iron is removed, or parenteral deferoxamine (less efficient, more complicated, expensive and hazardous).

■ Recent oral iron chelator: **deferasirox** is as effective as deferoxamine at reducing liver iron concentration and more convenient.

2-Cyanocobalamine= vitamine B12 (extrinsic factor).

It acts as a cofactor for several essential biochemical reactions

Deficiency:

Anemia, GI symptoms and neurologic abnormalities.

Chemistry:

▪ Prophyrin-like ring with a central cobalt atom attached to nucleotide.

▪ **Source:** meat (liver) , eggs, dairy products.

▪ For therapy use: cyanocobalamin and hydroxycobalamine.

Pharmacokinetics:

▪ Stored mainly in liver

▪ Normal daily requirement: 2-3 mcg.

▪ For its absorption, it makes a complex with intrinsic factor, a glycoprotein secreted by the parietal cells of the gastric mucosa and receptor mediated transport system in the lumen.

▪ It must be converted to active forms before absorption: Deoxyadenosyl-cobalamin and methyl-cobalamin.

▪ Vitamin B12 deficiency results from malabsorption of Vit B12 due to lack or loss or malfunction of intrinsic factor

▪ This intrinsic factor may be absent in gastrectomy and pernicious anemia.

▪ Nutritional deficiency (rare).

Route of administration:

▪ Mainly parenteral, IM, oral, aerosol

▪ Excretion: by kidney.

Pharmacodynamics:

▪ 2 essential enzymatic reactions require Vitamin B12:

1-Methylcobalamin as intermediate in the transfer of methyl group from N-methylTHF to homocysterine, forming methionine.

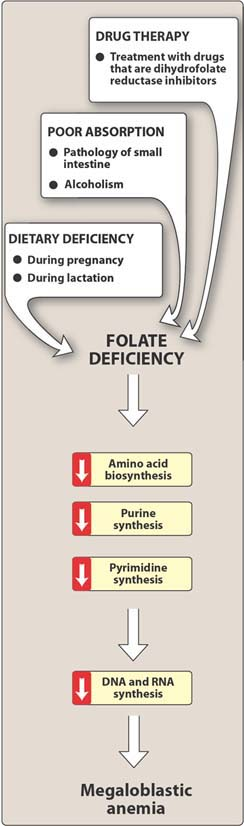
■ The depletion of THF prevents synthesis of adequate supply of adequate supply of deoxythymidylate (dTMP) and purine required for DNA synthesis.

**Treatment**: Vitamin B12 and folic acid.

2-Isomerization of methylmalonyl-CoA to succinyl CoA by methylmalonyl-CoA mutase In vit B12 deficiency: methylmalonyl-CoA accumulates

■ Neurologic manifestations due to disruption of methionine synthesis . treatment by vit B12 only.

Clinical Pharmocology

****Deficiency of vitamin B12

▪ Megaloblastic Anemia (macrocytic anemia + leukopenia & thrombocytopenia)

▪ Hematological abnormalities

▪ Hypercellular bone marrow with accumulation of megaloblastic erythroid

▪ Neurologic Syndrome: paresthesia and weakness in peripheral nerves, spasticity and ataxia

Causes of vitamin B12 deficiency

▪ Pernicious anemia (defective secretion of intrinsic factors by the gastric mucosal cells).

▪ Partial/total gastrectomy .

▪ Malabsorption Syndrome, inflammatory bowel syndrome or small bowel resection

▪ Damage of distal ileum that absorb vitamin B12 intrinsic factor complex

▪ Surgical resection of the ileum

Treatment

▪ Vitamin B12

▪Parenteral injection of vitamin B12 available as:

1- Cyanocobalamin.

2- Hydroxycobalamin is preferred (more highly protein-bound: longer duration of action).

Uses:

1- Pernicious anemia

2- Neurologic abnormalities

3- Gastrectomy

4- Cyanide poisoning

▪ **Initial therapy**: 100-1000 mcg of vitamin B12 IM daily or every other day for 1-2 weeks

▪ **Maintenance**: 100-1000mcg IM once a month for life

▪ Oral dose of 1000 mcg of vitamin B12 in pernicious anemia for patients who refuse or cannot tolerate the injection

▪ After parenteral administration, the vitamin can also administered as a spray/gel.

Adverse effect of vitamin B12

1- Allergic hypersensitivity reactions.

2- Arrhythmia secondary to hypo (K+)

3-Folic acid (FA):

-Reduce form: THFA is essential for the synthesis of amino acids, purines and DNA. Its deficiency is uncommon.-

-Deficiency of THFA causes anemia, congenital malformations in newborns and occlusive vascular disease

Chemistry:

▪ Folic acid is pteroglutamic acid, composed of a heterocycle (pteridine), P-aminobenzoic acid +glutamic acid

▪ Folic acid undergos reduction, catalyzed by DHFRase (dihydrofolate reductase), dihydroFA, THFA

▪ Vitamin B12 is required for activation of folic acid (demethylation)

Pharmacokinetics:

▪ **Source**: Yeast, liver, kidney, and green vegetables

▪ 5-20 mg of folates are stored in the liver

▪ Route: oral

▪ Converted to mono-glutamyl form and then absorbed in the proximal jejunum

▪ It is excreted in urine and stool

Pharmacodynamics:

▪ THFA Cofactor participate in one-C transfer reaction

▪ Produce dTMP needed for DNA synthesis.

▪ N-methylene THF is required for the vitamin B12 dependent reaction that generates methionine from hemocycteine

▪ THF cofactor donates 1 C until during synthesis of purine

Preparations:

▪ Synthetic Folic acid (tablets/parenteral)

▪ Folinic acid (active form)

Folic acid deficiency is caused by:

▪ Malabsorption and inadequate dietary intake of folate

▪ Alcohol dependence

▪ Liver disease

Clinical Pharmacology

▪ Folate deficiency leads to megaloblastic anemia

▪ (1 mg oral daily) will reverse megaloblastic anemia, restore normal serum folate, and replenish body store of folate

▪ Prophylactically, pregnant women and patients with hemolytic anemia who have increase folate requirements and may become folic acid deficient, especially if their diets are marginal

▪ Maternal folic acid deficiency will result in fetal neural tube defect such as spina bifida

▪ Patients who require renal dialysis

▪ **Drugs**: Methotrexate, trimethoprim and pyrimethamine inhibit DHFRase

▪ Deficiency of folate cofactors leads to megaloblastic anemia

▪ Long term use of phenytoin

▪ **High risk patients (those who need folic acid supplementation)**: pregnancy, premature infants, hemolytic anemia, liver disease, and renal dialysis

Hematopoietic Growth Factors

▪ Glycoprotein hormones regulate the proliferation and differentiation of hematopoietic progenitor cells in bone marrow.

▪ They can be produced by recombinant DNA technology.

# Erythropietin (Epotein)

Pharmacokinetics:

▪ IV / SC

▪ T½: 4-13 hrs in patient with chronic renal failure

▪ It is produced in the kidney

▪ It is not cleared by dialysis

▪ It is given 2-3 times weekly

▪ **Darbepoetin α:** is the glycosylate form, it has a longer half life

Pharmacodynamics:

▪ Stimulate erythroid proliferation and differentiation by interacting with specific erythropoietin receptors on erythrocyte progenitors

▪ Induces release of reticulocytes from bone marrow

▪ Tissue hypoxia stimulates erythropoietin synthesis

Clinical Pharmacology

▪ Anemia and chronic renal failure

▪ Erythropoietin is given at 50-150 IU/kg.

▪ IV/SC: Improve the hematocrit (in 10 days) and Hg level (in 2-6 weeks) and eliminate the need for transfusion

# Iron and Folic acid

▪ Anemia in HIV patients and zidovudine (anti HIV)

▪ Anemia in cancer patients

▪ Anemia due to bone marrow disorders, as in patients with aplastic anemia and other bone marrow failure states and multiple myeloma

▪ Anemias associated with chronic inflammation (RA)

▪ Anemia of prematurity.

▪ Accelerated erythropoiesis after phlebotomies.

▪ Misused by athletes to increase oxygen delivery and performance

Adverse effects and toxicity:

▪ Rapid increase of hematocrit and Hb leading to hypertension and thrombosis

▪ Seizure, headache

▪ Transient influenza-like syndrome

▪ Mild allergic reactions