Agents Used in Anemias

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Agents Used in Anemias Hematopoiesis: Requires a constant supply of: 1. Essential elements: Iron, vitamin B12 and folic acid. 2. Hematopoietic Growth Factors

Red = In severe anemia

- Yellowing
- Skin
- Paleness
- Coldness
- Yellowing
- Respiratory-
- Shortness of breath
- Muscular-
- Weakness
- Intestinal
- Changed stool color

Symptoms of Anemia

- Central
- Fatigue
- Dizziness
- Fainting

- Blood vessels - Low blood pressure

- Heart
 - Palpitations
 - Rapid heart rate
 - Chest pain
 - Angina
 - Heart attack Spleen - Enlargement

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IRON

Iron deficiency is the most common cause of chronic anemia.
 Causes microcytic hypochromic anemia.

Iron Content (mg)

		Men	Women
Hemoglobin		3050	1700
Myoglobin		430	300
Enzymes		10	8
Transport (transferrin)		8	6
Storage (ferritin and othe	r forms)	750	300
Total October 20	Munir Gharaibeh MD, PhD, I	4248	2314 5

Pharmacokinetics of Iron Free iron is toxic. All iron used to support hematopoiesis is reclaimed from catalysis of hemoglobin in senescent or damaged erythrocytes. Only a small amount of iron is lost from the body. **Possibile causes of Iron Deficiency:** Increased iron requirements Increased iron losses.

Absorption:

Daily intake: 10-15mg of elemental iron.
 Heme iron in meat hemoglobin and myoglobin is absorbed intact.

Iron from other sources is tightly bound to organic compounds and is less available and should be reduced to ferrous iron before it can be absorbed.

Daily absorption: 5-10% of the daily intake, usually from duodenum and proximal jejunum.

Absorption can increase in response to low iron or increased requirements.

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Absorption:

Divalent Metal Transporter (DMT1) actively transports ferrous iron across the luminal membrane of intestine.

Regulated by mucosal cell iron stores.

Ferroportin1(IREG1), transports iron across the basolateral membrane into the blood.

Excess iron is stored in the mucosa as *ferritin*, (a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of specialized protein called *apoferritin*).

Transport:

Transferrin (Tf) binds two molecules of iron in the plasma. The complex binds to Transferrin **Receptors (TfR)** on the maturing erythroid cells which internalize the complex through the process of receptormediated endocytosis. Iron is released for hemoglobin synthesis. Transferrin- transferrin receptor complex is recycled to the plasma membrane and transferrin dissociates and returns to the bersoma. Munir Gharaibeh MD, PhD, MHPE 9

Storage:

Ferritin(apoferritin AF and iron) is the storage form of iron. Stored in intestinal mucosa and in macrophages in the liver, spleen, and bone. Ferritin in serum is in equilibrium with storage ferritin and can estimate body iron stores.

Elimination:

There is no mechanism for excretion.
 Small amounts are lost by exfoliation of intestinal mucosal cells, bile, urine and sweat.

IRON THERAPY

Indications:

- Treatment and prevention of iron deficiency anemia:
- Increased requirements: infants, children, pregnant and lactating women, patients on hemodialysis, patients on erythropoietin treatment.
- Inadequate iron absorption: after gastrectomy, severe small bowel disease.
- Blood loss: acute or chronic, most common cause of iron pheficiency anemia.



IRON RICH FOODS

LENTILS KIDNEY BEANS SOY BEANS ALMONDS CASHEWS HAZELNUTS PUMPKIN SEEDS SESAME SEEDS

GUMES,

CLAMS

MEAT & FU

FRESH FRUITS: WATERMELON PEACHES APRICOTS

DRIED FRUITS: DATES PLUMS (PRUNES) FORTIFIED CEREALS OATMEAL CREAM OF WHEAT WHOLE GRAINS GINGERBREAD

4 GRAIN

BAKED POTATOES SWEET POTATOES BEETS & BEET GREENS SPINACH CHARD ASPARAGUS ARTICHOKES

TABL

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Oral Iron Preparations: Ferrous sulfate. Ferrous gluconate. **Ferrous fumarate.** -All are effective and inexpensive. -Can cause nausea, epigastric discomfort, cramps, constipation or diarrhea and black stools.

Parenteral Iron Therapy:

-Reserved for patients with documented iron deficiency who are unable to tolerate or absorb oral iron and for patients with extensive chronic blood loss who can not be effectively maintained with oral iron alone. -Carry the risk of iron overload.

Iron dextran:

- Given by deep IM injection or IV infusion.
- IM injection causes local pain and tissue staining.
- IV infusion causes hypersensitivity reactions: headache, fever, arthralgia, N, V, back pain, flushing, bronchospasm and rarely anaphylaxis and death.
- Iron-sucrose complex.
 Iron -sorbitol citrate" Jectofer".
 Iron sodium gluconate.
 Given only IV , less likely to cause hypersensitivity.

Acute Iron Toxicity:

Usually results from accidental ingestion by children as well as parenteral iron. 10 tablets can be lethal in children. Causes necrotizing gastroenteritis: vomiting, pain, bloody diarrhea, shock, lethargy and dyspnea. Patients may improve but may proceed to metabolic acidosis, coma and death.

Treatment of Acute Iron Toxicity:

Deferoxamine" Desferal": is a potent ironchelating compound which binds already absorbed iron and promotes its excretion in urine and feces.

- Whole Bowel Irrigation; to flush out unabsorbed pills.
- Activated charcoal is ineffective.
- Supportive therapy is also necessary.

<u>Chronic Iron Toxicity</u> = Hemochromatosis: Excess iron can deposit in the heart, liver, pancreas, and other organs leading to organ failure. Usually occurs in: **1. Inherited Hemochromatosis:** excessive iron absorption. 2. Patients with frequent transfusions e.g. in patients with Octobe Demolytic anemias 21

Treatment of Chronic Iron Toxicity: Intermittent phlebotomy(الفصد). Deferoxamine: is much less efficient than phlebotomy. Deferasirox" Exjade": oral, more convenient than deferoxamine.



Ball-and-stick model of two molecules of the iron-chelating drug deferasirox binding an atom of iron. Iron chelated in such a manner is unavailable to the fungi that cause mucormycosis.

 Image retrieved from http://en.wikipedia.org/wiki/Image:Deferasirox

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 Complex.png (5 April 2008).

Vitamin B₁₂

- Porphyrin-like ring with a central cobalt atom.
- Methylcobalamine
- Deoxyadenosyl cobalamine.
- Cyanocobalamine.
- Hydroxocobalamine.

Available in meat, liver, eggs, and dairy products.
 Nutritional deficiency only occurs in strict vertarians.

Vitamin B₁₂ Daily requirement : 2mcg Storage pool: 300-5000mcg. It would take about 5 years to exhaust all the stored pool and for megaloblastic anemia to develop after stopping absorption.

Pharmacokinetics of Vitamin B₁₂ Absorption requires the complexing with the: Intrinsic Factor(Castle's Factor), which is a glycoprotein secreted by the parietal cells of the stomach. Transported in the body by **Transcobalamine II**.

Schilling's Test:

 Measures absorption and urinary excretion of radioactively labeled Vitamin B_{12.}

Vitamin B₁₂ Deficiency Pernicious anemia. **Distal ileal disease e.g. Inflammation or** resection or Diphyllobothrium latum infestation. **Bacterial overgrowth of the small** intestine. Chronic pancreatitis. Thyroid disease. **Congenital deficiency of the intrinsic** factor. **Congenital selective Vitamin B₁₂** October 20 malabsorption from the Month of the Mark be in Jordan 37

Actions of Vitamin B₁₂

 Transfer of a methyl group from
 M⁵-methyltetrahydrofolate to homocysteine, forming methionine.
 N⁵-methyltetrahydrofolate is the major dietary and storage folate.

2. <u>Conversion of N⁵-methyltetrahydrofolate to</u> <u>tetrahydrofolate.</u> Deficiency leads to accumulation of N⁵methyltetrahydrofolate cofactors and depletion of tetrahydrofolate.

Vitamin B₁₂

Megaloblastic anemia of Vitamin B₁₂ deficiency can be partially corrected by ingestion of large amounts of folic acid. This is because folic acid can be reduced to dihydrofolate by the enzyme dihydrofolate reductase.

Actions of Vitamin B₁₂ **3. Isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme** methylmalonyl-CoA mutase. Vitamin B₁₂ depletion leads to the accumulation of methylmalonyl-CoA , thought to cause the neurological manifestations of Vitamin B₁₂ deficiency.

Enzymatic reactions that use vitamin B 1

A. Methyl transfer



B. Isomerization of L-Methylmalonyl-CoA



Therapy with Vitamin B₁₂ Parenteral :

Life-long treatment. Daily or every other day for 1-2 weeks to replenish the stores. Maintenance: injections every 1-4 weeks.

<u>Oral:</u>

Only for patients who refuse or can not tolerate injections.

<u>Intranasal:</u>

Four 20 patients in Mechanics, in Mere

Folic Acid

Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.
 Present in yeast, liver, kidney and green vegetables.

 Deficiency is common but easily corrected.
 Deficiency can result in: *Megaloblastic anemia*. Congenital malformations. Occlusive Vascular disease due to elevated homocysteine.

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Chemistry of Folic Acid Folic acid=Pteridine+ PABA+ **Glutamic acid.** Folic acid is reduced to Di and Tetra hydrofolate and then to folate cofactors, which are interconvertible and can donate one-carbon units at various levels of oxidation. In most cases folic acid is regenerated. Munir Gharaibeh MD, PhD, MHPE 34

The structure of folic acid



Kinetics of Folic Acid

- Readily and completely absorbed from the terminal jejunum.
- Glutamyl residues are hydrolyzed before absorption by a-1-glutamyltransferase (Congugase), within the brush border of the mucosa.
- N⁵-methyltetrahydrofolate is transported into the blood stream by active and passive processes.
- Widely distributed in the body.
- Inside cells, it is converted into THF by demethylation reaction in the presence of Vitamin B₁₂.

Kinetics of Folic Acid Only 5-20 mcg are stored in the liver. Excreted in urine and stool and also destroyed by catabolism. Megaloblastic anemia can develop within 1-6 months after stopping intake.

Actions of Folic Acid THF cofactors are important in onecarbon reactions: Production of dTMP from dUMP, which is needed in DNA synthesis. Generation of methionine from homocysteine. -Synthesis of essential purines.

Enzymatic reactions that use folates





Causes of Megaloblastic Anemia of Folic Acid Deficiency Inadequate dietary intake. Alcoholism, due to neglected nutrition. Liver disease causing impaired hepatic storage. Pregnancy and hemolytic anemia which increase the demand. Malabsorption syndrome. Renal dialysis. Drugs: Methotrexate, Trimethoprim and Phenytoin.

Treatment with Folic Acid Parenteral administration is rarely necessary because it is well absorbed orally even in malabsorption. 1 mg daily until cause is corrected. Or, indefinitely for patients with malabsorption or dietary inadequacy. Can be given prophylactically. Routinely given in early pregnancy or even before being pregnant. Recently supplemented to foods.