



In the name of Allah the Beneficent, the most merciful

We, the PharmaPill Team have tried our best to take all the doctor slides + his explanation .

We hope that this booklet will be most beneficial to you and we will post the notes on antihyperlipidemic drugs soon later...

Wishing you all the best,

PharmaPill team

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ANAEMIA

- Decrease Hemoglobin concentration
 - ✓ Decreased number of RBCs

CAUSES:-

- ☒ Blood loss (commonest cause) related to menstruation and child bearing.
- ☒ Increased demand as in growing children , lactating women.
- ☒ Deficiency of nutrients such as Iron, vitB12 , folic acid, vitC , pyridoxine and others.
- ☒ Reduced production or decreased response to erythropoietin (CRF, R. Arthritis, AIDS)
- ☒ Haemolysis (sickle cell disease)
- ☒ Diseases of the bone marrow (aplastic anemia)

TYPES OF ANEMIA:-

- Various classifications:

Examples:

- ☒ Iron deficiency anemia → microcytic , hypochromic
- ☒ Megaloblastic anemia → macrocytic , normochromic due to Vit. B₁₂ or Folic Acid deficiency
- ☒ Anemia due to decreased Erythropoietin as in chronic renal failure.

ANTI-ANEMIC DRUGS:-

- Drugs effective in iron deficiency and other hypochromic anemias:
 - ✓ Iron
 - ✓ Pyridoxine , Riboflavin , Copper
- Drugs effective in megaloblastic anemia:
 - ✓ Vitamin B₁₂
 - ✓ Folic Acid
- Hematopoietic growth factors:
 - ✓ Erythropoietin.



IRON:

Preparations:

- Oral:
 1. Ferrous sulphate
 2. Ferrous gluconate
 3. 3-Ferrous fumarate , etc.
- Parenteral:
 1. 1-Iron dextran → i.m or i.v
 2. 2-Iron Sorbitol → i.m only.

Pharmacokinetics:-

- Absorption depends on :
 - requirements
 - iron stores
 - Ferrous (Fe^{++}) / ferric (Fe^{+++}) form
 - pH (it has poor absorption in neutral PH)
 - ✓ in stomach it binds to mucoproteins in presence of Vitamin C to get absorbed
 - Chelators or complexing agents
 - Malabsorption syndrome

Distribution:

- **Transferrin** : A beta-globulin , transport iron in plasma, specifically bind ferric iron.

Storage:

- Apoferritin + ferric hydroxide ⇌ **Ferritin** (the storage form of iron in intestinal mucosal cells & cells of reticuloendothelial systems).

**Excretion:**

- No mechanism for excretion of iron
- Small amounts lost by exfoliation of intestinal mucosal cells into stool.
- Trace amounts excreted in bile , urine , & sweat.

Uses:

- **Prevention and treatment of iron deficiency anemia, as in:**
 1. Pregnant , lactating , or menstruating women
 2. Growing children & adolescence
 3. Infants , especially premature infants
 4. Malabsorption ---- gastrectomy , severe small bowel disease.
 5. Occult G.I. bleeding ----- G.I. Cancer
 6. Dietary deficiency

Adverse effects of Oral iron therapy

- ☒ Nausea , abdominal pain , & either constipation or diarrhea.

Acute Oral toxicity (overdose ; poisoning)

- ☠ Necrotizing gastroenteritis with vomiting, abdominal pain, bloody diarrhea
- ☠ Shock , lethargy & dyspnea
- ☠ Severe metabolic acidosis
- ☠ Coma
- ☠ Death

Treatment:

- Whole bowel irrigation
- Desferrioxamine (Deferoxamine)
 - ✓ orally for Unabsorbed iron
 - ✓ Parenteral (i.m. , i.v.) for iron absorbed

Desferrioxamine + ferric iron ➡ **Ferrioxamine** (excreted in urine and bile).



Chronic iron toxicity (iron overload)

e.g., in:

- ☑ Hemochromatosis
- ☑ Hemolytic anemias
- ☑ Thalassaemia with transfusional overload

Hemosiderosis:

- ✓ a focal or general increase in tissue iron stores without associated tissue damage

Hemochromatosis:

- ✓ associated with tissue damage

Treatment:

- Intermittent Venesection (Phlebotomy) => when there is no anemia
- Chelation (Desferrioxamine) => for transfusional overload

Adverse effects of Parenteral iron therapy

- 💀 Local pain & tissue staining – (brown discoloration of tissue overlying the injection site).
- 💀 Headache , light-headedness , fever , arthralgias,
- 💀 nausea , vomiting , back pain , flushing , urticaria , bronchospasm
- 💀 Rarely anaphylaxis & death



VITAMIN B₁₂:

■ FEATURES OF VITAMIN B₁₂ DEFECIENCY

- Impairment of DNA synthesis affects all cells but most apparently RBCs.
 - a. Megaloblastic Anemia
 - b. GI symptoms
 - c. neurologic abnormalities

Neurological abnormalities:

- 💡 Symptoms may be psychiatric & physical. Degeneration of brain and spinal cord (Subacute combined degeneration) and peripheral nerves.
- 💡 Paresthesia & weakness in peripheral nerves spasticity, ataxia, & other CNS dysfunction

Chemistry

- Porphyrin-like ring with a central cobalt atom & nucleotide.
- Cobalamins = various organic groups covalently bound to cobalt atom

📌 Active forms of vitamin B₁₂ in human:

- 1) Deoxyadenosylcobalamin
- 2) Methylcobalamin

📌 Vitamin B₁₂ available for therapeutic uses:

- 1) Cyanocobalmin
 - 2) Hydroxycobalamin
 - ✓ Hydroxycobalamin is preferred because it is highly protein-bound & therefore remains longer in the circulation.
- ✓ Cyanocobalamin, hydroxycobalamin & other cobalamin (found in food sources) are converted to active forms Deoxyadenosylcobalamin & methylcobalamin



Pharmacokinetics:

Absorption:

- **Intrinsic factor (IF)** : a glycoprotein , secreted by parietal cells of gastric mucosa
- **IF-Vit.B₁₂ Complex** absorbed by active transport in the distal ileum

☐ Transported in plasma bound to the **glycoprotein transcobalamin II** &

☐ is taken up by **tissues where required** or stored in **hepatocytes**

Route of administration:

- **Mostly Parenteral** (i.m).
- **Oral**
- **Aerosol**

Elimination:

- ☐ not significantly metabolized
- ☐ pass into bile
- ☐ Enterohepatic circulation
- ☐ Excreted via kidney

Uses

- **Pernicious (addisonian) anemia**
- **After partial or total gastrectomy**
- **Malabsorption syndromes**
- **Insufficient dietary intake**

☐ Hydroxycobalamin (Not cyanocobalamin)

- **Tobacco Amblyopia**
- **Cyanide toxicity**



Adverse effects

- ☠ Allergic hypersensitivity reactions
- ☠ Antibodies to hydroxycobalamin-transcobalamin II complex
- ☠ Arrhythmias secondary to hypokalemia

Precautions / contraindications

- ☠ Undiagnosed vit. B₁₂ deficiency / megaloblastic anemia
- ☠ Cyanocobalamin : leber's disease , tobacco amblyopia



FOLIC ACID (PTEROYLGLUTAMIC ACID; VITAMIN B₉):

- Is inactive : Active form is ---- **tetrahydrofolic acid**

Functions

- Is required for synthesis of Amino acids , purines, pyrimidines, & DNA ; & therefore in the cell division.

Features of folic acid deficiency

- Mitotically active tissues such as erythroid tissues are markedly affected.
- **megaloblastic anemia**
- Congenital malformations → neural tube defects (e.g. spina bifida)
- Vascular disease
- Vitamin C deficiency can cause **megaloblastic anemia**

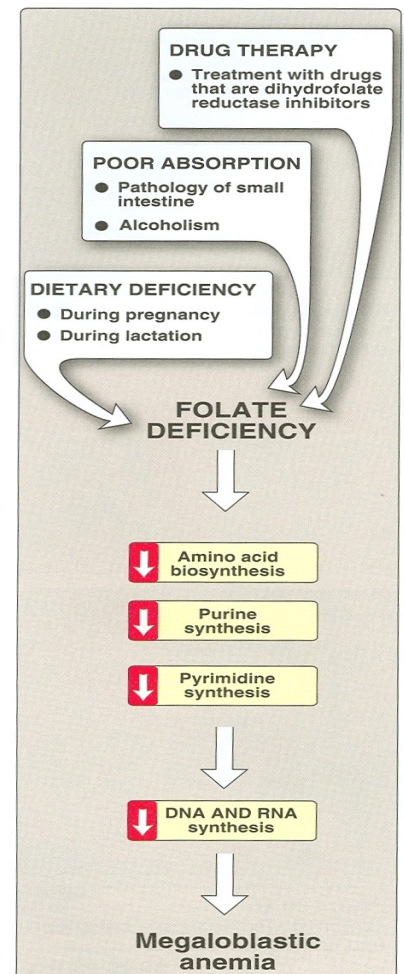


Figure 20.27
Causes and consequences of folic acid depletion.



Pharmacokinetics

- **Route of administration** : usually oral
- In diet : Polyglutamate form
- For absorption must be converted to Mono-glutamyl form
- Absorbed mostly in **proximal jejunum**
- Transported to tissues bound to a **plasma-binding protein**
- Excreted in urine & stool
- Also destroyed by catabolism
- Hepatic reserves sufficient for only 1-6 months

Uses

- **Prevention & treatment of folic acid deficiency**

- ☐ Dietary insufficiency (e.g. in elderly)
- ☐ Pregnancy & lactation
- ☐ to prevent → Congenital malformations → neural tube defects (e.g., spina bifida)
- ☐ High red cell turn over → e.g. in hemolytic anemias
- ☐ Premature infants
- ☐ Malabsorption syndromes
- ☐ Drugs that folic acid should be coadministered with them:
 - ✓ Antiepileptics → enzyme inducers
 - ✓ Phenytoin
 - ✓ Primidone
 - ✓ Phenobarbitone
 - ✓ Antimalarials
 - ✓ pyrimethamine
 - ✓ Methotrexate

FOLINIC ACID (not folic acid)

Uses:

- ☐ Myelofibrosis
- ☐ Exfoliative dermatitis
- ☐ Rheumatoid arthritis
- ☐ Malignant disease , e.g., lymphoma
- ☐ Chronic hemodialysis



Adverse effects

- Generally well tolerated:
 - ☛ Rarely : G.I. Disturbances , hypersensitivity reactions , Status epilepticus may be precipitated

Precautions / contraindications

- ☛ Undiagnosed Folic acid deficiency / megaloblastic anemia



ERYTHROPOIETIN (EPOTEIN):

a glycoprotein hormone produced (90%) by peritubular cells in kidney & remainder by liver and other tissues

- is essential for normal reticulocyte production
- synthesis is stimulated by hypoxia
- synthesized for clinical use by recombinant DNA technology.

Pharmacokinetics

- Route of administration : S.C. or I.V.
- Plasma $t_{1/2}$: 4 - 13 hrs in patients with chronic renal failure.
- Not cleared by dialysis

Mechanism of action

- increases rate of stem cell differentiation
- increases rate of mitosis in red cell precursors, blast-forming units, colony forming cells
- increases release of reticulocyte from marrow
- increases Hb synthesis
- its action requires adequate stores of iron



Uses

- 1) Anemia associated with chronic renal failure
- 2) premature infants
- 3) Anemia during chemotherapy of cancer
- 4) Anemia of AIDS (which is exacerbated by zidovudine treatment)
- 5) to increase the yield of autologous blood before donation
- 6) Anemia of chronic inflammatory conditions such as rheumatoid arthritis
- 7) MISUSED --- by sports people

Adverse effects

- Usually due to excessive increase in hematocrit
 - 💀 increase blood pressure
 - 💀 thrombosis
 - 💀 seizures
 - 💀 headache
 - 💀 hypertensive crises with encephalopathy-like symptoms
 - 💀 clotting in dialyser
 - 💀 Transient influenza-like symptoms → chills & myalgias
 - 💀 iron deficiency
 - 💀 transient increases in platelet count
 - 💀 hyperkalemia
 - 💀 skin rashes
 - 💀 pure red cell aplasia → discontinue the drug
 - 💀 antibodies to epoetins



Precautions / contraindications

- 💀 hypertension should be well controlled
- 💀 seizures
- 💀 thrombocytosis
- 💀 ischemic vascular disease
- 💀 iron , folic acid , vit. B₁₂ supplements may be needed
- 💀 heparin during dialysis

Monitor

- hematocrit.
- blood pressure.
- platelet count.
- serum potassium.



Revision

Anemia

- Anemia (reduced blood RBCs count or hemoglobin concentration) can be due to many causes.
- Most important of these causes are:
 - ✓ Iron deficiency.
 - ✓ Vitamin B-12 (cobalamin) deficiency.
 - ✓ Folic acid deficiency.
 - ✓ Erythropoietin deficiency.

IRON DEFICIENCY:

- Results in microcytic hypochromic anemia.
- Iron is better absorbed in acidic pH.
- Pregnancy, lactation, growth, malnutrition or congenital malabsorption are frequent causes of iron deficiency.
- It is treated by commercial formulas of iron e.g. Oral (ferrous sulfate, gluconate and fumarate), Parental (iron dextran and iron sorbitol)
- Adverse effects of these formulas may be:
 - Hypersensitivity reactions ranging from mild aches and pigmentations up to bronchospasm, flushing and urticaria.
 - GIT symptoms such as gastroenteritis, vomiting, constipation or diarrhea may result.
- Overdoses of these formulas can cause
 - Chronically: diseases such as haemochromatosis and siderosis.
 - Acutely: severe signs such as hemorrhagic diarrhea, dyspnea and acidosis may result.
- Chelators administration and GIT irrigation may be effective in treating iron overdose.



VITAMIN B-12 (COBALAMIN) DEFICIENCY:

- Results in macrocytic megaloblastic anemia.
- GIT disturbances causes Vit.B-12 deficiency due to the requirement of the intrinsic factor for its absorbance.
- Oral, parenteral-I.M. or aerosol preparations are available for the treatment of the deficiency.
- The active forms of Vit.B-12 found in the body are: methyl-cobalamin and deoxyadenosyl-cobalamin.
- The forms found in the supplements are: hydroxy-cobalamin and cyano-cobalamin.
- Adverse effects of these supplements may be:
 - Hypersensitivity.
 - Hypokalemia (arrhythmias).
 - Antibody formation against hydroxy-cobalamin and cyano-cobalamin.

N.B. Iron is almost NOT excreted in the bile & the urine.

Vit.B 12 & folic acid ARE excreted in the bile & the urine.

FOLIC ACID DEFICIENCY:

- Results in macrocytic megaloblastic anemia.
- It is usually seen in pregnant, lactating, hemolytic, malabsorption, and growing patients.
- Folic acid deficiency may be due to haemodialysis or may be caused by some autoimmune diseases such as rheumatic arthritis, malignancies and bone marrow diseases.
- Its active form in the body is tetrahydrofolate.
- It is supplemented as polyglutamate which is transformed into monoglutamate upon absorption.
- The supplement is given orally and is absorbed in the proximal jejunum.
- Adverse effects of its usage include:
 - Hypersensitivity, GIT disturbances.



ERYTHROPOIETIN DEFICIENCY:

- It is usually caused by autoimmune diseases, cancers or by chronic renal failure.
- It is supplemented as erythropoietin which is given I.M. or S.C.
- It is NOT removed by haemodialysis.
- Adverse effects include:
 - Hypertension.
 - Thrombosis.
 - Neurologic symptoms.
 - ↑ hematocrit.