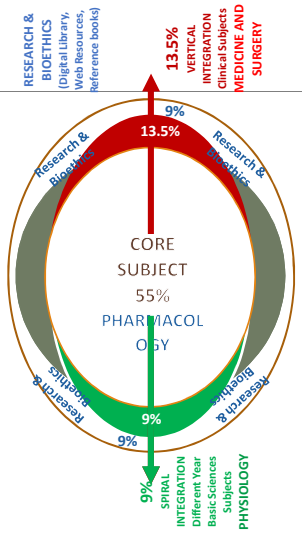
MOTTO AND VISION

To impart evidence based research oriented medical education

To provide best possible patient care

To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology LGIS (65 slides)	
Core Subject – 70%	
Horizontal Integration	
Vertical integration (Clinical Subjects)	Medicine (15 %)
Spiral Integration – 10%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

HEMATINICS

- SPIRAL INTEGRATION ANATOMY/ PHYSIOLOGY

THE HAEMATOPOIETIC SYSTEM

HEMATOPOIESIS: Production of blood cells i.e. RBC'S, WBC'S & platelets from undifferentiated stem cells &

- Sites where hematopoiesis occurs, known as hemopoietic tissues or organs (bone marrow, lymph nodes, thymus, liver, spleen)
- Hematopoietic machinery requires constant supply of—**iron, vitamin B_{12}, folic acid** & **hematopoietic growth factors**
- Inadequate supplies of essential nutrients or growth factors result in deficiency of functional blood cells

ANEMIA

Anemia, a deficiency in oxygen-carrying erythrocytes or reduced hemoglobin content in blood

- Different types of anemias, based on red cell size & Hb content & microscopical examination :
- *Hypochromic*, *microcytic anemia* (small RBCs with low Hb)
- *Macrocytic anemia* (large RBCs, few in number)
- *Normochromic normocytic anemia* (fewer normal-sized RBCs, with normal Hb content)
- Mixed pictures

Core subject –
Pharmacology

HEMATINICS

HEMATINICS: agents used to increase hemoglobin content of blood OR to treat anemias

- ✓ Iron
- ✓ Vitamin B_{12} (Cobalamin)
- ✓ Folic acid
- ✓ Erythropoietin

IRON

DISTRIBUTION OF IRON IN BODY

- Total body iron in an adult: 2.5–5 g (average 3.5 g)
- More in men (50 mg/kg) than in women (38 mg/kg)
- Distributed into:

  Hemoglobin (Hb) : 66%

  Myoglobin (in muscles) : 3%

  Heme enzymes (e.g., cytochromes, catalase & peroxidase): 6%

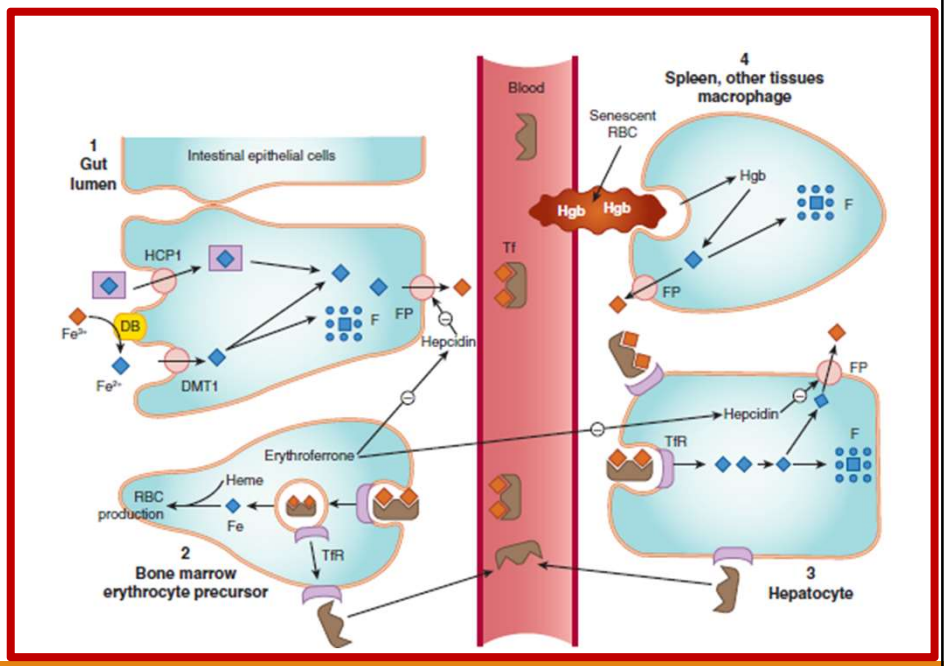
  Stored as ferritin & hemosiderin: 25%

PHARMACOKINETICS

Site of absorption: duodenum, proximal jejunum, distal small intestine

- 0.5–1 mg daily absorbs from diet (↑absorption in menstruating & pregnant women)
- Dietary iron, present either as heme or as inorganic iron
- Heme iron in meat hemoglobin & myoglobin efficiently absorbed, without first dissociated into elemental iron
- Nonheme iron or inorganic iron (in *ferric* form) especially in vegetables & grains, reduced by a ferrireductase to ferrous iron (Fe^{2+}) before absorbed by intestinal mucosal cells

ABSORPTION TRANSPORT AND STORAGE OF IRON



PHARMACOKINETICS

ELIMINATION

- In faeces, small amounts by shedding of mucosal cells containing ferritin
- In bile, urine, & sweat
- About 1 mg lost daily

IRON PREPARATIONS

ORAL IRON

- Ferrous sulphate
- Ferrous gluconate
- Ferrous fumarate
- Colloidal ferric hydroxide

PARENTERAL IRON

- Iron dextran
- Iron sucrose
- Sodium ferric gluconate
- Ferric Carboxymaltose

- VERTICLE INTEGRATION MEDICINE/ SURGERY

IRON DEFICIENCY ANEMIA

Causes of iron deficiency anemia are:

- ✓ Inadequate dietary intake of iron (nutritional iron deficiency)
- ✓ Blood loss from GI tract, menorrhagia
- ✓ Malabsorption: gastrectomy, small bowel disease

Signs & symptoms of iron deficiency anemia, pallor, fatigue, dizziness, exertional dyspnea, tachycardia, increased cardiac output & vasodilation

INDICATION FOR IRON USE

IRON DEFICIENCY ANEMIA: most important indication for iron use

Most commonly seen due to increase requirement in:

- ✓ Infants, especially premature infants & growing children
- ✓Pregnant & lactating women
- ✓Patients with chronic renal disease

TREATMENT OF IRON DEFICIENCY

THERAPY WITH ORAL IRON

- Ferrous sulfate, treatment of choice for iron deficiency
- **DOSE**: 200-400 mg of elemental iron /day in pts with iron deficiency
- About 25% of oral iron given can be absorbed
- Duration of treatment: (3–6 months) after correction of cause

ADVERSE EFFECTS OF ORAL IRON

- Nausea, epigastric discomfort, abdominal cramps
- Constipation & diarrhoea
- Staining of teeth, metallic taste
- Black stool (Can mask occult GIT blood loss)

Reduce side effects by:

- Reducing the dose
- Taking Tab. immediately after or with meals
- Changing salt preparation

TREATMENT OF IRON DEFICIENCY

THERAPY WITH PARENTERAL IRON

Indications for use are:

- Pts unable to tolerate oral iron
- Pts unable to absorb oral iron b/c of malabsorption syndromes, inflammatory bowel disease & post gastrectomy
- Pts with chronic renal failure or with chemotherapy-induced anemia & receiving treatment with erythropoietin
- In presence of severe iron deficiency with chronic bleeding

THERAPY WITH PARENTERAL IRON

IRON DEXTRAN, colloidal solution with ferric oxyhydroxide & dextran polymers containing 50 mg elemental iron/ml

- ***Only preparation that can be given IM as well as IV***
- Should be given after test dose

Adverse effects of iron dextran therapy:

- Local pain & tissue staining with IM route
- **I/V administration:** Hypotension, tachycardia, headache, fever, arthralgias, nausea, vomiting, back pain, flushing, urticaria, bronchospasm
- Rarely, anaphylaxis & death

THERAPY WITH PARENTERAL IRON

- ***Sodium ferric gluconate complex & Iron-sucrose complex***
- Both given by IV route
- Less hypersensitivity reactions than iron dextran
- Monitoring with parenteral iron preparation to avoid toxicity/ overload

ACUTE IRON TOXICITY

- Seen in young children who accidentally ingest iron tab (10 tab of any oral iron preparations can be lethal)

Signs & Symptoms of toxicity:

- Necrotizing gastroenteritis with vomiting, abdominal pain, bloody diarrhea
- Followed by shock, lethargy & dyspnea
- May be followed by severe metabolic acidosis, coma & death

TREATMENT OF ACUTE IRON TOXICITY

To prevent further absorption of iron from gut

- Induce vomiting or **whole bowel irrigation** to flush out unabsorbed pills
- Give egg yolk & milk orally: to complex iron

To bind and remove iron already absorbed

- ***Deferoxamine,*** iron-chelator, given IV to bind already absorbed iron & promote its excretion in urine & feces
- Supportive therapy for gastrointestinal bleeding, metabolic acidosis & shock

CHRONIC IRON TOXICITY OR IRON OVERLOAD

- Occurs in chronic hemolytic anemias, requiring frequent blood transfusions, such as *thalassaemias*
- Inherited *haemochromatosis* (a genetic iron storage disease with increased iron deposition in heart, liver, pancreas, & other organs → organ failure & death

TREATMENT:

- Intermittent phlebotomy, one unit of blood can be removed every week until all excessive iron removed
- If not managed by phlebotomy, Iron chelation therapy by parenteral **deferoxamine** or oral iron chelators ***Deferasirox*** or ***Deferiprone*** may be given

VITAMIN B_{12}

- SPIRAL INTEGRATION ANATOMY/ PHYSIOLOGY

VITAMIN B_{12}

- Also called **Extrinsic factor** to differentiate it from **intrinsic factor**
- **Cyanocobalamin & hydroxocobalamin** are converted to active forms
- Vit B_{12} produced only by microorganisms & humans obtain by ingesting foods of animal origin
- Dietary source: Meat (especially liver), eggs & dairy products
- Nutritional deficiency rare, may seen in strict vegetarians after many years without meat, eggs, or dairy products

Core subject –
Pharmacology

PHARMACOKINETICS

- Normal daily requirements of Vit B_{12} about 2 mcg
- Stored primarily in liver
- Only trace amounts of Vit B_{12} lost in urine & stool
- Vit B_{12} is absorbed after forming complexes with **intrinsic factor**
- Intrinsic factor–Vit B_{12} complex absorbed in distal ileum
- Transported to various cells of body by transcobalamin I, II & III
- Vit B_{12} deficiency results from malabsorption of Vit B_{12} either due to lack of intrinsic factor or loss or malfunction of absorptive mechanism in distal ileum

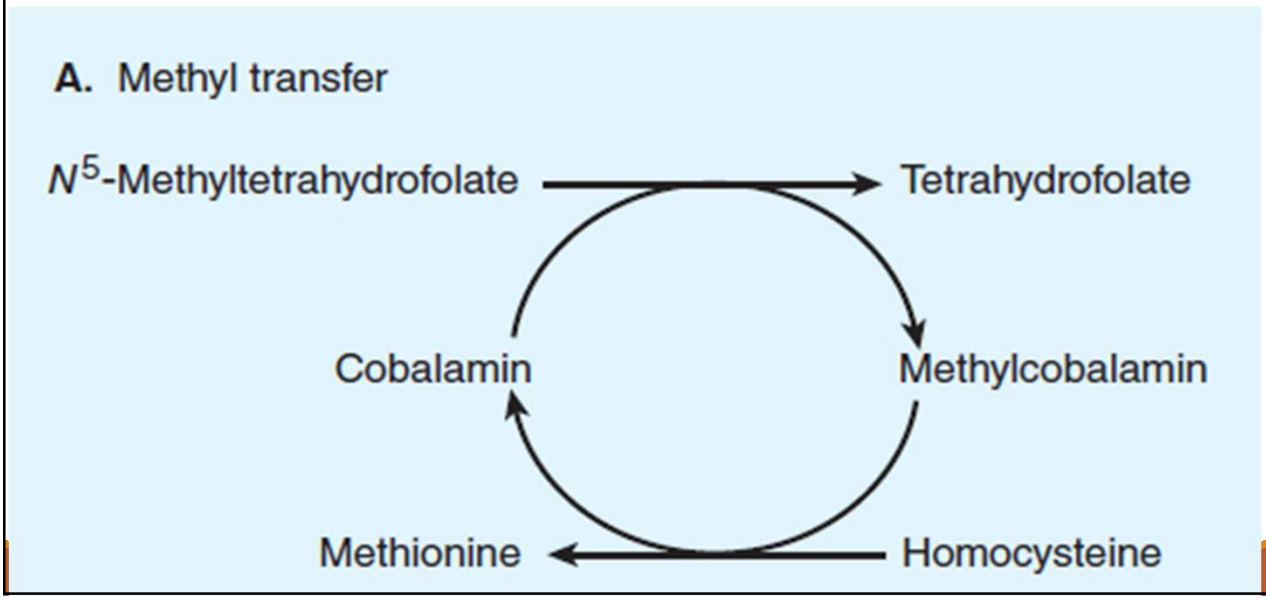
MECHANISM OF ACTION

Vit B_{12} is required for two main biochemical reactions in humans

1- Conversion of methyl-FH4 to FH4

- This reaction involves conversion of both methyl-FH4 to tetrahydrofolate(FH4) & homocysteine to methionine
- Methyl group from methyl-FH4 transferred first to Vit B_{12}& then to homocysteine to form methionine
- Vit B_{12} deficiency inhibits conversion of methyl-FH4 to FH4 → deficiency of folate cofactors needed for synthesis of deoxythymidylate (dTMP) & purines for DNA synthesis

Enzymatic reactions that use vitamin B_{12}



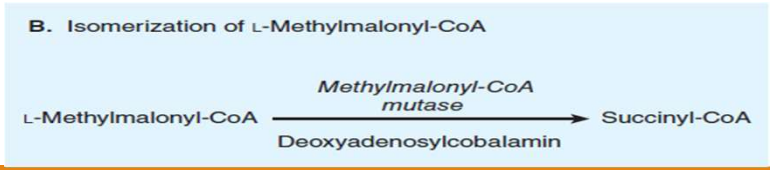
MECHANISM OF ACTION

- Accumulation of folate as methyl FH4 & depletion of tetrahydrofolate cofactors in Vit B_{12} deficiency known as ***Methylfolate trap***
- Megaloblastic anemia due to Vit B_{12} deficiency can corrected by giving folic acid
- Vit B_{12} deficiency causes accumulation of homocysteine
- Rise of homocysteine levels, →↑ risk of atherosclerotic cardiovascular disease
- Increase serum homocysteine levels used for diagnosis of Vit B_{12} deficiency

MECHANISM OF ACTION

2- Isomerization of methylmalonyl-CoA to Succinyl-CoA

- An important reaction in carbohydrate & lipid metabolism
- In Vit B_{12} deficiency, this conversion cannot take place & methylmalonyl-CoA, accumulate
- Increase serum & urine concentrations of methylmalonic acid support diagnosis of Vit B_{12} deficiency
- Accumulation of methylmalonyl-CoA may responsible for neurologic manifestations of Vit B_{12} deficiency



- VERTICLE INTEGRATION MEDICINE/ SURGERY

CAUSES OF VITAMIN B_{12} DEFICIENCY

- **Pernicious anemia:** an autoimmune disorder which results in destruction of gastric parietal cells → absence of intrinsic factor in gastric juice → inability to absorb Vit B_{12}
- **Malabsorption**: Post gastrectomy, terminal ileal resection, inflammatory bowel disease (Crohn's disease), Chronic pancreatitis
- **Other causes:** Gastric mucosal damage, e.g. chronic gastritis, gastric carcinoma
- **Nutritional deficiency:** less common cause; may occur in strict vegetarians
- **Drugs:** Metformin, Proton pump inhibitors, Ethanol, Phenytoin
- **Increased demand:** pregnancy, infancy

CLINICAL MANIFESTATION OF VITAMIN B_{12} DEFICIENCY

- **Megaloblastic, macrocytic anemia** associated mild or moderate leukopenia or thrombocytopenia
- **Neurologic manifestations:** paresthesias in peripheral nerves with tingling or numbness of fingers & toes, difficulty in walking, ataxia, mood changes, depression, memory loss, disorientation & in severe cases dementia
- **Gastrointestinal side effects:** including sore tongue, stomach upset, weight loss, diarrhea or constipation

DIAGNOSIS OF VIT B_{12} DEFICIENCY

- Measuring serum levels of vitamins
- Methylmalonic acid (MMA)—help detect mild or early Vit B_{12} deficiency , if B_{12} is low, MMA generally high
- Schilling TEST:
  - ✓ Measure absorption & urinary excretion of radioactive Vit B_{12}
- Detect cause of Vit B12 deficiency, Defective Intrinsic factor secretion or due malabsorption from distal ileum

THERAPEUTIC INDICATIONS

- Treatment of megaloblastic anemia along with folic acid
- Treatment of pernicious anemia along with intrinsic factor
- Prophylactically, in strict vegetarians, patients who had gastrectomy, & small bowel resection
- Mega doses can be used in neuropathies
- Hydroxocobalamins, in cyanide poisoning

THERAPY WITH VITAMIN B_{12}

PARENTERAL PREPARATIONS:

- Cyanocobalamin
- Hydroxocobalamin, preferred(Highly protein bound), With better retention in blood
- Route: I/M
- **Initial therapy:** 100–1000 µg of Vit B_{12}IM daily or every other day for 1–2 weeks to replenish body stores
- **Maintenance therapy:** consists of 100–1000 µg IM once a month
- If neurologic abnormalities persist, give Vit B_{12} injections every 1–2 weeks for 6 months before switching to monthly injections
- Oral Vit B_{12}–intrinsic factor mixtures, 1000 µg given to treat patients with pernicious anemia who refuse or cannot tolerate injections

FOLIC ACID

- SPIRAL INTEGRATION ANATOMY/ PHYSIOLOGY

FOLIC ACID

- Folic acid is composed pteridine, *p*-aminobenzoic acid & glutamic acid
- Inactive as such, reduced to coenzyme form in two steps:

FA → Dihydrofolate → Tetrahydrofolate by folate dihydrofolate reductase enzyme

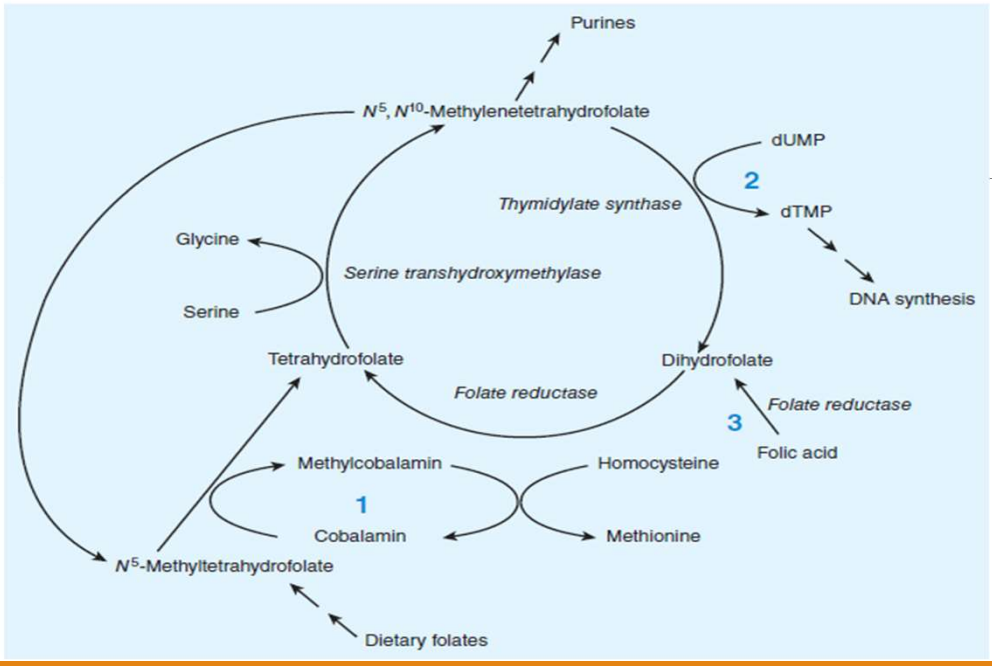
- ***Daily requirement*** < 0.1 mg for adult
- During pregnancy, lactation 0.8 mg/day

PHARMACOKINETICS

- ***Dietary sources:*** yeast, liver, kidney & green vegetables
- Dietary folates readily & completely absorbed in proximal jejunum
- Transported in blood as methyl-THFA, inside cells, methyltetrahydro-folate converted to tetrahydrofolate by reaction that requires vitamin B_{12}
- 5-20mg, stored in liver & other tissues
- Excreted in urine & stool

METABOLIC FUNCTIONS

- ***Tetrahydrofolate's main function is transporting single-carbon groups*** (methyl, methylene or formyl group) in metabolic processes
- ***Synthesis of Thymidylate:*** Methylene tetrahydrofolate required for biosynthesis of dTMP (deoxythymidine monophosphate) from dUMP (deoxyuridine monophosphate) conversion catalyzed by thymidylate synthase.
- ***Conversion of Homocysteine to Methionine:*** Methylene tetrahydrofolate required for Vitamin B_{12}-dependent reaction that generates methionine from homocysteine



METABOLIC FUNCTIONS

- ***Synthesis of Purines***
- ***Conversion of Serine to Glycine***
- ***Histidine Metabolism***

DIAGNOSIS OF FOLIC ACID DEFICIENCY

- By measuring serum folate levels or red blood cell folate levels

➢ VERTICLE INTEGRATION MEDICINE/ SURGERY

FOLATE DEFICIENCY

Occurs due to:

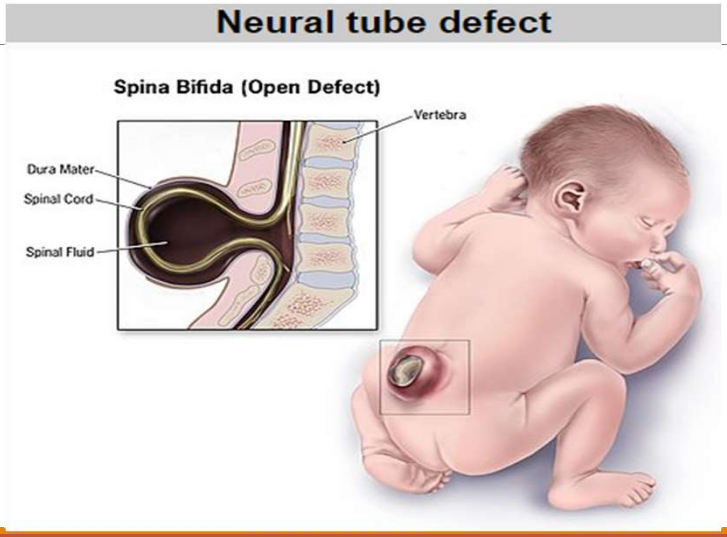
- Inadequate dietary intake of folates
- Malabsorption syndromes like celiac disease
- Chronic alcoholism & liver disease
- **Increased demand:** pregnancy, lactation, rapid growth periods, hemolytic anemia
- Patients who require renal dialysis

Drug induced: Methotrexate, trimethoprim, pyrimethamine, phenytoin, phenobarbitone, primidone & oral contraceptives

MANIFESTATIONS OF FOLIC ACID DEFICIENCY

- **MEGALOBLASTIC ANAEMIA:**
- Develops more rapidly by deprivation of folate, than Vit B_{12} deficiency, reflecting limited body stores of folate
- **Epithelial damage:** glossitis, enteritis, diarrhea
- **Neural tube defects,** including spina bifida in offspring, due to maternal folate deficiency
- **Hyperhomocysteinemia** (elevations in plasma homocysteine), risk factor for coronary artery & peripheral vascular disease & for venous thrombosis

SPINA BIFIDA



Core subject –
Pharmacology

THERAPEUTIC USE OF FOLATE

- ***Megaloblastic anemia:*** 1 mg folic acid orally daily
- ***Prophylaxis of folate deficiency:*** in high-risk patients like pregnant women, alcoholics, hemolytic anemia, liver disease, & patients on renal dialysis
- ***Treatment or prevention of toxicity from dihydrofolate reductase inhibitors*** (*methotrexate, pyrimethamine & trimethoprim*) ***folinic acid***—also known as *leucovorin calcium* is used as an antidote against various antifolate drugs

ERYTHROPOIETIN

- SPIRAL INTEGRATION ANATOMY/ PHYSIOLOGY

ERYTHROPOIETIN

- Hormone produced by peritubular cells of kidney
- Anemia & hypoxia are sensed by kidney cells & induce rapid secretion of EPO
- Erythropoietin binds to receptor on surface of erythroid progenitors in marrow
- Stimulates erythroid proliferation & differentiation
- Releases reticulocytes in circulation
- Induces hemoglobin formation & erythroblast maturation

Results → correction of the anemia

ERYTHROPOIETIN

- An inverse relationship exists between Hb level & serum erythropoietin level
- If Hb levels fall & anemia becomes more severe, serum erythropoietin level rises
- **Important exception to this inverse relationship:** in anemia of chronic renal failure, erythropoietin levels usually low b/c kidneys cannot produce erythropoietin
- Exogenous erythropoietin not useful for treating aplastic anemia and leukemias b/c endogenous erythropoietin levels are high in these situation

➢ VERTICLE INTEGRATION MEDICINE/ SURGERY

ERYTHROPOIETIN PREPARATIONS

RECOMBINANT HUMAN ERYTHROPOIETIN

Epoetin alfa: half-life of 4–13 hours, administered 3 times a week

Darbepoetin alfa: modified form of erythropoietin, longer half-life than epoetin alfa, administered weekly

Epoetin beta: long-lived recombinant product, administered as a single IV or S/C dose at 2-week or monthly intervals

CLINICAL INDICATIONS

Treatment of anemia in:

- Patients with chronic renal failure
- HIV-infected patients treated with zidovudine
- Cancer patients treated with myelosuppressive cancer chemotherapy
- Preoperatively for patients undergoing elective, noncardiac, nonvascular surgery
- ***Used illegally by athletes to increase their Hb levels ("blood doping") & improve performance***
- **This misuse resulted in deaths of several athletes & strongly discouraged**

ADVERSE EFFECTS

- Most common hypertension & increase risk of cardiovascular events, thromboembolic events, stroke, (due to increases in blood viscosity & peripheral vascular resistance)
- **Pure red cell aplasia (PRCA)** accompanied by neutralizing antibodies directed against erythropoietin which inactivate endogenous hormone as well as recombinant drug
- PRCA, seen in patients treated by epoetin alfa subcutaneously for a long period

BIOETHICS

Exogenous erythropoietin is used illegally by athletes to increase their Hb levels ("blood doping") & improve performance

This misuse resulted in deaths of several athletes & strongly discouraged

RESEARCH ARTICLE

https://pubmed.ncbi.nlm.nih.gov/9726380/

https://pubmed.ncbi.nlm.nih.gov/13009494/

MCQs

1. The megaloblastic anemia that results from vitamin B12 deficiency is due to inadequate supplies of which of the following?

A) Cobalamin

B) dTMP

C) Folic acid

D) Homocysteine

E) Methyltetrafolate

MCQs

Which of the following is most likely to be required by a 5 year old boy with chronic renal insufficiency?

A) Cyanocobalamine

B) Deferoxamine

C) Erythropoietin

D) Filgrastim

E) Oprelvekin

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