بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 3

Folic acid deficiency and hematopoietic growth factor



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Hematopoietic Growth Factors

What stimulates blood cell lineages to proliferate? Growth factors.

Hematopoietic Growth Factors

- **The hematopoietic growth factors are glycoprotein hormones that regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.**

Erythropoietin

- **Formed by the kidney in response to tissue hypoxia (severe anemia)**

It is a growth factor that stimulates the growth and proliferation of red blood cell (RBC) progenitor cells and It is produced by the kidneys in response to tissue hypoxia.

Causes of Tissue Hypoxia:

1. Severe anemia
2. Smoking
3. High altitude

- Smoking reduces oxygen delivery to tissues, stimulating erythropoietin production in the kidneys. This leads to increased RBC production and elevated hemoglobin levels (secondary polycythemia). Consequently, blood viscosity increases, which may increase the risk of thrombosis. Increased RBC mass may also cause facial plethora (a reddish appearance of the face).

Erythropoietin

Synthesized by recombinant DNA technology

- **Recombinant human Erythropoietin is available for use (epoetin alpha).**

Pharmacodynamics:

1. **It stimulates erythroid proliferation and differentiation by interacting with specific receptors on red cell progenitors.**
2. **It induces release of reticulocytes from bone marrow.**

- The response to anemia treatment can be assessed by measuring hemoglobin levels and **reticulocyte count**. An increased reticulocyte count indicates that the bone marrow is responding to treatment, even if the hemoglobin level is still below the target value.

Erythropoietin

3. **It corrects the anemia (provided that bone marrow response is not impaired by iron deficiency, primary bone marrow disorders, or bone marrow suppression from drugs or chronic diseases).**

- Before starting treatment,all possible causes of anemia and associated deficiencies should be investigated, because the presence of another deficiency may prevent an adequate response to treatment.

- The bone marrow acts as a factory for blood cell production. Therefore, if an underlying pathology affects the bone marrow (primary bone marrow disorders), its response to treatment may be inadequate.

- Regarding drug induced bone marrow suppression, **anticancer drugs (chemotherapy)** are common causes. They suppress bone marrow activity and can affect the production of different blood cell lineages, leading to anemia, thrombocytopenia, neutropenia, and other cytopenias.

Erythropoietin

4. Normally, an inverse relationship exists between the hematocrit and erythropoietin level. This is NOT true in anemia of chronic renal failure.

Normally,there is an inverse relationship between hematocrit (Hct) and erythropoietin (EPO) levels:
When hematocrit is high, erythropoietin levels are low.
When hematocrit is low, erythropoietin levels increase.

However, this relationship does not occur in anemia of chronic renal failure.Since the kidneys are responsible for erythropoietin production, impaired kidney function leads to inadequate erythropoietin production despite the presence of anemia and tissue hypoxia.

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سبحان الله العظيم

Erythropoietin

Clinical Pharmacology:

- **Used for anemia of chronic renal failure, NOT other types of anemia where endogenous erythropoietin is usually high.**
- **Iron and folate supplementation may be required in cases of inadequate response.**

Erythropoietin

Adverse Effects:

1. **Most common are those associated with rapid rise of hemoglobin and hematocrit: hypertension and thromboembolic complications.**

The rapid increase in hemoglobin and hematocrit leads to increased blood viscosity, which may result in elevated blood pressure (hypertension) and thromboembolic complications. These are among the most common and serious adverse effects of erythropoietin therapy.

For that reason when you treat anemia of chronic renal disease:

Hemoglobin levels should not be increased > 11 g/dL because of risk of serious cardiovascular events, thromboembolic events, stroke, and mortality.

2. **Infrequent and mild allergic reactions.**

Although epoetin alfa is a human protein, it is produced using recombinant DNA technology in host cells, such as bacteria or other cells. During the manufacturing process, small amounts of foreign proteins from the host cells may remain in the final preparation if they are not completely removed during purification. These residual foreign proteins may trigger allergic reactions.

Myeloid Growth Factors

Myeloid Growth Factors

- **Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF).**
- **Recombinant human G-CSF (rHuG-CSF):**
  Filgrastim **Stim**; stand for "stimulation"
- **Recombinant human GM-CSF (rHuGM-CSF):**
  Sargramostim

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Myeloid Growth Factors

Pharmacodynamics:

- **They stimulate proliferation and differentiation by interacting with specific receptors found on myeloid progenitor cells.**

1. G-CSF stimulates proliferation and differentiation of progenitors committed to the neutrophil lineage. Filgrastim is a G-CSF preparation used to stimulate neutrophil production in patients with neutropenia, particularly in cases of chemotherapy induced neutropenia.

It also activates the phagocytic activity of mature neutrophils and prolongs their survival in the circulation.

, allowing them to survive longer than their normal lifespan.

Myeloid Growth Factors

2. **GM-CSF has broader biologic actions than G-CSF.**

- **It is a multipotential hematopoietic growth factor that stimulates proliferation and differentiation of early and late granulocytic, erythroid and megakaryocyte progenitors.**

Myeloid Growth Factors

Clinical Pharmacology:

1. Cancer Chemotherapy-Induced Neutropenia.

- **G-CSF and GM-CSF accelerate the rate of neutrophil recovery and reduces the duration of neutropenia after dose-intensive myelosuppressive chemotherapy.**

Doctor's Explanation:

Intensive myelosuppressive chemotherapy can cause significant neutropenia, which increases the risk of infections due to the reduced number of neutrophils and the patient's immunosuppressed state. These infections may progress to bloodstream infections and sepsis, potentially becoming life threatening if not recognized and treated promptly. **Clinical manifestations may include:**

1. Fever.
2. Signs and symptoms related to the site of infection.
3. Malaise and fatigue.

However infections in neutropenic patients may occur without fever or obvious clinical signs. Sometimes, the patient may only experience general fatigue and malaise, making the infection difficult to recognize. This is particularly important because chemotherapy itself can also cause fatigue, potentially masking the symptoms of an underlying infection.

- Therefore, patients with neutropenia require careful monitoring and appropriate management to prevent serious infectious complications.

Myeloid Growth Factors

Adverse effects:

1. **Bone pain.**

Myeloid growth factors stimulate the proliferation of bone marrow cells, causing increased pressure within the bone marrow (intramedullary pressure), which results in bone pain.

2. **Fever, arthralgias, myalgias.**

even in the absence of infection. They may also cause joint pain (arthralgia) and muscle pain (myalgia).

3. **Capillary leak syndrome characterized by peripheral edema, and pleural or pericardial effusions.**

4. **Allergic reactions.**

5. **Splenic rupture.**

due to stimulation of splenic cells. In rare cases, the enlarged spleen may rupture, which is an acute surgical emergency that can lead to peritonitis.

Megakaryocyte Growth Factors

- **Thrombopoietin and interleukin-11 (IL-11) are endogenous regulators of platelet production.**
- That's why IL-11 is considered as a growth factor
- **Thrombopoietin agonists: Romiplostim and Eltrombopag.**
- **Recombinant form of IL-11: Oprelvekin.**

Megakaryocyte Growth Factors

Eltrombopag: this drug isn't a first choice

- **It is an orally active small nonpeptide thrombopoietin agonist used for therapy of patients with chronic immune thrombocytopenia who have had an inadequate response to other therapies (steroids, immunoglobulins, or splenectomy).**

Thrombocytopenia= decrease in platelet amount

Further explanation :
An **agonist** is a substance that binds to a receptor and activates it, producing a biological response.
Thrombopoietin (TPO) is a natural hormone, mainly produced by the liver. Its function is to stimulate the bone marrow to produce platelets.
It does this by binding to the thrombopoietin receptor (TPO-R or c-Mpl), which is present on megakaryocyte progenitor cells and megakaryocytes.

- **Etrombopag is not a first choice therapy for chronic immune thrombocytopenia, we have to try steroids, immunoglobulins, or splenectomy first and if they didn't work, Etrombopag is given.**

The indications are specific, not generalized

Megakaryocyte Growth Factors

- **It is also used for treatment of thrombocytopenia in patients with hepatitis C to allow initiation of interferon therapy.**

Romiplostim:

- **It is used for therapy of patients with chronic immune thrombocytopenia.**

Further explanation :
Interferon therapy uses IFNs to resist viruses, it's used in Hepatitis C to trigger immune response.
But this therapy can cause thrombocytopeina because it affects the bone marrow

Megakaryocyte Growth Factors

Adverse effects:(mainly)

Eltrombopag:

1. **Hepatotoxicity.**
2. **Portal vein thrombosis.**

There is more side effects

Megakaryocyte Growth Factors

Romiplostim: *the worst*

1. Portal vein thrombosis.
2. In patients with myelodysplastic syndromes, it increases the blast count and risk of progression to acute myeloid leukemia.
3. Bone marrow fibrosis. Can't produce any type of cell
4. Rebound thrombocytopenia after stopping the drug administration.

Megakaryocyte Growth Factors

Oprelvekin:

1. **Fatigue,**
2. **Transient atrial arrhythmias.**
3. **Anemia (due to hemodilution).**
4. **Dyspnea (due to fluid accumulation in the lungs).**difficulty in breathing
5. **Hypokalemia (due to diuretic therapy for fluid retention).**

Folic Acid Deficiency Anemia

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Folic Acid

- **Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.**

The consequences of folate deficiency include:

1. **Megaloblastic anemia.** in adults or children
2. **Congenital malformations** in infants **– neural tube defects, such as spina bifida and anencephaly,**
3. **Occlusive vascular disease due to homocysteine accumulation.** Can involve in thrombosis

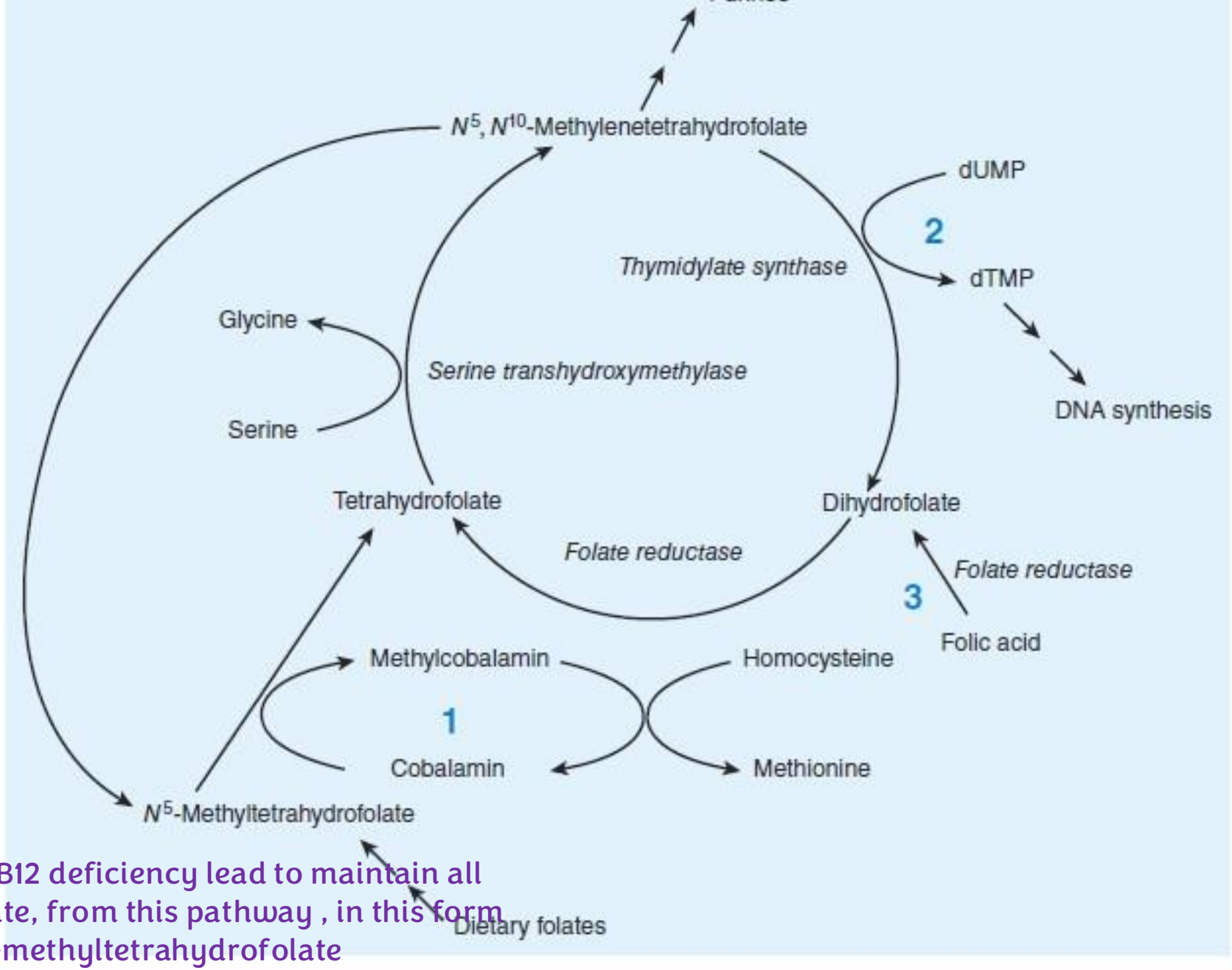
Folic Acid

- **Folic acid (pteroylglutamic acid) can exist in the form of monoglutamate, triglutamate and polyglutamate.** polyglutamate is the storage form of folic acid in the body in the liver and other tissues
- **It undergoes reduction by folate reductase to dihydrofolate and tetrahydrofolate.** If we give folic acid directly

dihydrofolate and tetrahydrofolate are active forms

Folic Acid

- **Tetrahydrofolate can be transformed to folate cofactors.**
- **The folate cofactors are inter-convertable and serve the donation of one-carbon units at various level of oxidation.**



Vit.B12 deficiency lead to maintain all folate, from this pathway , in this form N5-methyltetrahydrofolate

URE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}–dependent reaction that allows most dietary fol
nter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the deoxythymidine
nophosphate (dTMP) cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows

Folic Acid

Pharmacokinetics:

- **Food rich in folic acid include yeast, liver, kidney & green vegetables.**

1. **Folic acid is absorbed in the proximal jejunum** if there is a disease in the site of absorption this will affect the absorption process .
2. **Usual daily absorption from diet ~ 50-100 µg, depending on metabolic requirements.**
3. **Pregnant women may absorb up to 300-400 µg daily.** The absorption increases with increased requirement

Folic Acid

4. **Normal tissue storage in liver and other tissues ~ 5-20 mg.**
5. **If folic acid absorption stops, megaloblastic anemia develops in 1-6 months.**

storage/ daily absorptoion ---> so it takes 1-6 months to consume the whole stored folic acid

Folic Acid

this slide isn't required but only the amounts in the previous slide

Daily Requirements:

- **Infants (0–6 months): 65 µg / day**
- **Infants (7–12 months): 80 µg / day**
- **Children (1–3 years): 150 µg / day**
- **Children (4–8 years): 200 µg / day**
- **Children (9–13 years): 300 µg / day**
- **Teens (14+ years) and Adults: 400 µg / day**
- **Pregnant Women: 600 µg / day**
- **Breastfeeding / Lactating Women: 500 µg / day**



Folic acid

Clinical pharmacology:

1. **Megaloblastic anemia. Vitamin B_{12} deficiency must first be excluded. Why?** Because folic acid can correct megaloblastic anemia but cannot correct the neurological deficit in Vit.B12 deficiency (you think you treat the anemia but the neurological damage continues)
2. **Prevention of folic acid deficiency in high risk groups such as pregnancy, alcohol dependence, hemolytic anemia, …**

- **Usually used orally until the cause is removed and stores are replenished**.treat the anemia and return the storage

Folic acid

Causes of deficiency:

Drugs that causeLoss of appetite hepatotoxicity lead to Lose the appetite--> poor diet

1. **Inadequate dietary intake.**
2. **Liver disease**(damage the stores) **and alcohol dependence because of diminished stores and poor diet.**

Lactation

3. **Increased requirements: pregnancy, hemolysis**
4. **Malabsorption syndromes.** A problem in absorption site
5. **Renal dialysis.** Because folic acid is dialysable

Folic acid

6. **Drugs:**

A. **Methotrexate**(anticancer), **trimethoprim. ,pyrimethamine**(antibiotics) Commonly used

inhibit dihdrofolate reductase

B. Long-term phenytoin therapy impair folate absorption also calcium--> cause osteopenia

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			