Pharmacology HLS

Lecture 2+3

By farah al hasanat

Iron

Treatment

Elemental iron per tablet	Tablet size (mg)	Prepararion
65	325	Ferrous sulfate hydrated
36	325	Ferrousl gluconate
106	325	Ferrous fumarate

24

Oral Iron Preparations

and about 25% of iron given as ferrous sulfate can be absorbed.

200- 400 mg of elemental iron should be given daily for → 3-6 months after correction → to correct the anemia and replenish iron stores.

Adverse effects:
- Nausea,
- epigastric discomfort
- abdominal pain
- constipation
- diarrhea → Most common than diarrhea
- Black stools → هاي لازم نعالج بالاول اذا في bleeding عشان ما نخريط هو من اعراض الدواء ولا هو السبب بنقص الحديد

These effects are dose-related and can be : 1) reduced by lowering the dose
2) giving it with meals or immediately after meals.

2. Parenteral iron therapy:

Should be reserved for patients:
- 1) Unable to tolerate oral iron.
- 2) Unable to absorb oral iron.
  - Malabsorption syndromes → What are foods that hinder absorption of iron?
    - 1-Calcium as supplement or any diary product
    - . 2-The whole grains , tea
    - 3-metals such as zinc they compete with the transport of iron so we don't give metal supplements at the same time with iron supplements
    - 4-drugs that reduce acidity of the stomach which is need for reduction of iron to Fe+2.
    - drugs such tetracycline it forms complex with the ion thus decrease absorption, they both decrease absorption of each other(iron & tetracycline).
    - PPI also such as
      - omeprazole
      - lamsoprazole
      - esmoprazole
  - small bowel resection → colon cancer patient so we resect part of the colon which is responsible for iron absorption.
- 3) With extensive chronic blood loss not acute blood loss because we give patients blood transfusion

Form
- Iron dextran:
  - ferric hydroxide
  - low- molecular-weight
  - containing 50 mg elemental iron/mL of solution
  - Given by:
    - Iv
      - causes hypersensitivity reactions
      - headache
      - fever
      - arthralgia
      - backpain
      - flushing
      - bronchospasmand
      - rarely anaphylaxis and death
    - Im → causes local pain and → tissue staining
- Iron sodium gluconate.
  - Given only IV
  - less likely to cause hypersensitivity.
- · Iron-sucrose complex.

Toxicity

Acute Iron Toxicity:
- General:
  - Usually results from accidental ingestion by children as well as parenteral iron
  - Patients may improve but may proceed to metabolic acidosis, coma and death.
  - Causes necrotizing gastroenteritis → vomiting, pain, bloody diarrhea, shock, lethargy and dyspnea صعوبة في التنفس
  - 10 tablets can be lethal in children
- Treatment of Acute Iron Toxicity: → Deferoxamine
  - : is a potent iron- chelating compound
  - which binds already absorbed iron → promotes its excretion in urine and feces
  - Whole Bowel Irrigation → to flush out unabsorbed pills
  - Activated charcoal is ineffective → Activated charcoal can be used to absorb the drugs form the stomach and intestine but in iron toxicity it's ineffective
  - Supportive therapy is also necessary. → Supportive therapy means to correct other symptoms suchas acidosis,pHimbalance

Chronic Iron Toxicity= Hemochromatosis:
- General → Excess iron can deposit in
  - heart
  - Liver
  - Pancreas
- Usually occurs in:
  - 1. Inherited Hemochromatosis → excessive iron absorption.
  - Patients with frequent transfusions → in patients with hemolytic anemias
- Treatment of Chronic Iron Toxicity
  - Intermittent phlebotomy → Donating blood from time to time or more frequently for patients with inherited diseases like inherited hemochromatosis
  - Deferoxamine → is much less efficient than phlebotomy.
  - Deferasirox → oral, more convenient than deferoxamine.

Vitamin B12

General

- Its deficiency leads to
  - gastrointestinal symptoms
  - neurological abnormalities
  - anemia
- It consists
  - porphyrin-like ring
  - central cobalt atom — attached to the nucleotide

Active forms are:

1. Deoxyadenosylcobalamin
2. Methylcobalamin

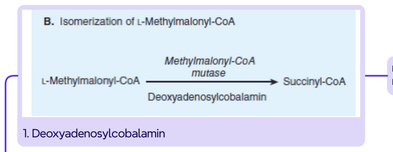
Pharmacokinetics:

- Vitamin B12, in physiologic amounts is absorbed only after it complexes with the intrinsic factor
  - The intrinsic factor-vitamin B12 complex is absorbed in the terminal ileum
    - by a highly specific receptor- mediated endocytosis
  - * glycoprotein secreted by the parietal cells of the gastric mucosa
- Daily absorption ~ 1-5 µg
- Vitamin B12 is stored mainly in the liver with an average normal storage pool of 3-5 mg.
- Daily requirements are ~ 2 µg
- How long would it take for the storage pool to be depleted and symptoms of deficiency to appear?
  - If we have 4mg =4000 micrograms so it needs nearly about 6 years to be depleted . But Vit B12 still common—— because of the malabsorption(defect of intrinsic factor).
- Only trace amounts are lost in urine and stool
- Once absorbed it is transported in the body bound to a plasma glycoprotein, transcobalamin II.

Pharmacodynamics

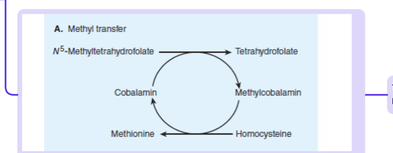
2 essential enzymatic reactions in humans:

1. Deoxyadenosylcobalamin



- responsiblefor the isomerization of methylmalonyl-CoA
  - to succinyl-CoA
    - deficiency in contrast to accumulation of methylmalonyl-CoA
  - By methylmalonyl- CoA mutase.

2. Methylcobalamine



- transfer of a methyl group from N5-methyltetrahydrofolate
  - to homocysteine to form :
    - methionine
      - cause of neurological manifestations of Vitamin B12
    - tetrahydrofolate (THF).
      - the precursor of many folate cofactors.
      - In Vitamin B12 deficiency, folate cofactors become deficient leading to defects in several biochemical reactions involved in the transfer of one-carbon groups.
      - Vitamin B12 deficiency can be partially corrected by large doses of folic acid, which is converted to dihydrofolate and then to THF by folate reductases.
      - will NOT correct neurological manifestations, but will largely correct the anemia.

Causes of deficiency:

Malabsorption of Vitamin B12 due to:

1. Lack of intrinsic factor
2. Loss or malfunction of the terminal ileum
3. Strict vegetarians (long-term):
   - The vitamin is NOT synthesized by animals or plants
   - The ultimate source is microbial synthesis
   - Mainly present in meat (liver), eggs and dairy products.
   - It has to be released from these sources before absorption.
4. Atrophic gastritis — (from Helicobacter pylori)
5. Lack of gastric HCl — (cobalamin is NOT released from protein)
6. Drugs
   - PPI — decrease acidity in case of peptic ulcer and other condition which hinder Vit B12 absorption
   - Metformin

Clinical Pharmacology: B12 supplements

Clinical Pharmacology: B12 supplements

1. Treatment of pernicious anemia
2. Treatment of neurological manifestations of Vitamin B12 deficiency.

Drug

- cyanocobalamin
- Hydroxocobalamin — preferred because it is more highly protein-bound (high half-life) and remain longer in the circulation.
  - Used as parenteral injection of, both to replenish stores and maintenance, usually for life

Main Topic 7

Folic Acid

General

- Reduced forms of folic acid are required for
  - synthesis of amino acids, purines and DNA.
- Forms
  - pteroylglutamic acid can exist in the form of
    - monoglutamate
    - triglutamate
    - polyglutamate
- undergoes reduction by folate reductase
  - dihydrofolate
  - tetrahydrofolate
    - can be transformed to folate cofactors possessing one-carbon
      - inter-convertable and serve the donation of one-carbon units at various level of oxidation.
- Normal tissue storage in liver and other tissues ~ 5-20 mg.
- Folic acid is absorbed in the proximal jejunum

The consequences of folate deficiency include:

- 1. Megaloblastic anemia
  - If folic acid absorption stops, megaloblastic anemia develops in 1-6 months
- 2.Congenital malformations
  - neural tube defects, such as spina bifida and anencephaly
- 1. Occlusive vascular
  - disease due to homocysteine accumulation

Pharmacokinetics:

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

Clinical pharmacology:

- 1. Megaloblasticanemia.VitaminB12 deficiencymust first be excluded
- . 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.

Causes of deficiency

- 1. Inadequate dietary intake
- 2. Liver disease and alcohol dependence because of diminished stores and poor diet.
- 3. Increased requirements: pregnancy, hemolysis
- 4. Malabsorption syndromes
- 5. Renal dialysis. غسيل الكلى
- 6. Drugs:
  - A. Methotrexate,
    - trimethoprim, pyrimethamine

    inhibit dihydrofolate reductase
  - B. Long-term phenytoin therapy impair folate absorption ادوية الصرع

Erythropoietin

General

- Formed by the kidney in response to tissue hypoxia (severe anemia)
- 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
- deficiency, primary bone marrow disorders, or bone marrow suppression from drugs or chronic diseases).
- inverse relationship exists between the hematocrit and erythropoietin level. This is NOT true in anemia of chronic renal failure.

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
  - to accommodate the high synthesis of RBCs after giving EPO

Adverse Effects:

- 1. Most common are those associated with rapid rise of
  - hematocrit
  - hemoglobin
    - Hemoglobin levels should not be increased > 11 g/dL because of risk of serious cardiovascular events, thromboembolic events, stroke, and mortality.
      - hypertension and thromboembolic complications.
- 2. Infrequent and mild allergic reactions.
  - Before we were using EPO extracted from animals , that may cause allergic reaction. Now with recombinant form we don't have these allergic reactions.