Antianemic drugs
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I. DRUGS USED IN THE THERAPY OF IRON DEFICIENCY ANEMIA

1. ORAL IRON THERAPY

PREPARATIONS OF IRON SALTS

Preparation	Dose[mg]	Fe^{++}content [mg]	%Fe
Ferrous sulfate	325	65	20
Ferrous fumarate	300	99	33
Ferrous gluconate	300	35	11
Feostat chew tabs	100	33	33
Slow-release ferrous sulfate	525	105	20

Oral ferric maltol (non-salt based)

- ❑ does not cause nausea, bloating, and constipation, as typically observed with salt-based therapies
- ❑ an option for patients with inflammatory bowel disease or chronic kidney disease
- ❑ worse absorption compared to ferrous forms

Recommended dosage of elemental iron/day

- prophylaxis and mild nutritional iron deficiency - **50 - 100** mg/day;
- prevention of iron deficiency during pregnancy – **60** mg/day
- treatment of iron deficiency anemia – **60-200 mg/**day
- children weighing 15-30 kg can take half the average adult dose; small children, infants - 5mg/kg; up to 60mg/day

ADJUVANTS:

1. to enhance iron absorption – ascorbic acid (to maintain iron in ferrous state);
2. to decrease side effects – stool softeners (docusate sodium)

The timing of dose – to achieve maximal absorption, iron salts should be taken between meals or on an empty stomach.
to avoid absorption problems, consider an iron supplement once daily with a meal containing meat protein and with a vitamin C supplement tablet

Duration of treatment

goals of the therapy:
(1) recovery of Hb
(2) creation of iron stores (women: 500mg, men:1000mg)
the duration of the therapy is dependent on the severity of anemia (Hb is synthesized at **maximal rate of 2-2.5g/liter of whole blood/day) – average time of treatment 4-6 months**

UNTOWARD EFFECTS OF ORAL IRON PREPARATIONS

- heartburn**,** nausea**,** upper gastric discomfort**,** constipation or diarrhea**,** black stool**,** liquid preparations may cause tooth staining

ACUTE IRON TOXICITY

- initial symptoms include: vomiting, diarrhea, abdominal pain
- these symptoms may be followed in 12 to 24 hours by shock, coma and metabolic acidosis.
- death may occur in 12 to 24 hours after ingestion

TREATMENT OF ACUTE IRON OVERDOSE

1. induction of vomiting
2. precipitation of iron in the upper GI tract by lavage with sodium bicarbonate or phosphate solution.
3. deferoxamine (im, iv) – agent which may chelate iron ions – non-absorbable from the GI tract;, metabolized principally by plasma enzymes; excreted in urine; given im/iv; *Untoward effects* allergic reactions, dysuria, abdominal discomfort, diarrhea, fever, hypotonia, and tachycardia; *Contraindications*: renal insufficiency and anuria

Shock, dehydratation and acid-base abnormalities should be treated in the conventional manner.

CHRONIC IRON TOXICITY, HEMOCHROMATOSIS

Damages: heart, liver, pancreas – store excess iron
Causes:
1. Individuals with inherited abnormality of iron absorption
2. Frequent transfusions
3. Long-term parenteral iron therapy
Treatment:
Phlebotomy, deferasirox, deferoxamine

DEFERASIROX

an orally active chelator that is selective for iron (as Fe3+)
Indications:

- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older

Side effects:

- acute renal failure, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders
- gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts
- hepatic injury, including hepatic failure and death

CAUSES OF ORAL THERAPY FAILURE:

- noncompliance
- misdiagnosis (e.g. inflammation)
- malabsorption

- continuing blood loss equal to or greater than the rate of RBC production

Malabsorption diagnosis:
Fe levels every 30 min for 2h after administration of 50mg of ferrous sulfate; Increase by >50% - absorption adequate

2. PARENTERAL IRON THERAPY
The indications to parenteral iron therapy:

1. malabsorption syndrome, patient receiving total parenteral nutrition.
2. uncorrectable iron losses that are too great to be replaced by oral therapy
3. gastrointestinal disorder, such as inflammatory bowel disease, in which symptoms may be aggravated by iron preparations
4. patient who cannot tolerate oral iron preparations
5. patients with Chronic Kidney Disease (CKD)-related anemia treated with EPO
6. noncompliant patient
7. patients with chronic heart failure (with anemia and low ferritin level)

i.m. administration:
local reactions include: skin staining, pain, inflammation, sterile abscesses, necrosis, atrophy, fibrosis
i.v. administration is preferred to i.m. administration in patients: (1) who have limited muscle mass available for an i.m. injections, (2) with impaired absorption from the muscle (e.g. edema), (3) at risk for uncontrolled bleeding (e.g. hemophilia, trombocytopenia, anticoagulation therapy), (4) when large doses are indicated for therapy.

DOSAGE

Most commonly the total dose of iron (i.m., i.v.) is calculated using the following equitation (Ganzoni):

Total iron deficit [mg] =
body weight [kg] x (target Hb-actual Hb) [g/dl] x 2.4 + depot iron [mg]

to calculated dose of iron we should add amount of iron for recovery of iron stores (depot iron - 500mg for women, 1000mg for men)

ADVERSE REACTIONS TO PARENTERAL IRON THERAPY:

1. Anaphylactic reactions (in approximately 0,3% of patient) **iron-dextran>>sodium ferric gluconate, iron sucrose**
2. Other hypersensitivity reactions (utricaria, rashes, dyspnea, sweating, dizziness, arthralgia, myalgia, and fever)
3. Delayed reactions –(24 to 48 h after i.v. or 3-7 days after i.m.): malaise, arthralgia, backache, chills, high fever, headache, myalgia, nausea and vomiting.
4. Phlebitis - prolonged infusion of a concentrated solution or when intramuscular preparation containing 0,5 % phenol is used in error
5. Exacerbation of the disease in some patients with rheumatoid arthritis treated with iron-dextran - a delayed hypersensitivity reaction to the dextran

Caution should be used in patient who have a history of a significant allergic or asthma.
Examples of preparations:
Iron-dextran (*Dexferrum*) – stable complex of ferric hydroxide and low-molecular-weight dextrane; iv, im; 50mg/ml
Iron-sucrose (*Venofer*) – iv; 20mg/ml (anemia caused by CKD)
Iron sodium gluconate complex (*Ferrlecit*) – iv; 12.5mg/ml (anemia caused by CKD)
Ferumoxytol (*Feraheme*) – superparamagnetic iron oxide coated with polyglucose sorbitol carboxymethylether iv; 30mg/ml; 510mg of Fe/infusion over 5 min

Agent	Typical single adult dose
Low molecular weight iron dextran	1000 mg
Ferric carboxymaltose	750 mg
Ferumoxytol	510 mg
Ferric derisomaltose	1000 mg

II. THERAPY OF MEGALOBLASIC ANEMIA
1. Vitamin B_{12}-deficiency anemia
CAUSES OF VITAMIN B_{12} DEFICIENCY

1. Inadequate intake (vegetarian) rare
2. Malabsorption (Food-Bound Cobalamin Malabsorption (FBCM); drugs)
3. Pernicious anemia
4. Following **total gastrectomy** or extensive damage to gastric mucosa
5. Congenital absence or functional **abnormality of IF** (rare)Competition for cobalamin: **fish tapeworm** (competition by the worm for cobalamin) **bacteria-blind loop syndrome** - colonization of the small intestine by large masses of bacteria which divert cobalamin from the host.Vitamin B_{12}-deficiency is recognized by its impact on: **the hemopoetic, gastrointestinal and the nervous systems**.

The hematologic manifestations:

- impaired **DNA replication** - production of morphologically abnormal cells and death of cells during maturation (megaloblastic erythropoiesis);

- in the peripheral blood - many cell fragments, *poikilocytes* and *macrocytes*; MCV >110 fl
- *pancytopenia* - severe deficiency,
- **clinical manifestation**: weakness, vertigo, palpitation, angina, symptoms of heart failure

The gastrointestinal manifestation:

- sore tongue (smooth and beefy red), anorexia with moderate weight loss, diarrhea
- latter manifestation: megaloblastosis of the small intestinal epithelium – malabsorption

The neurological manifestation:

- demyelization followed by axonal degeneration and neuronal death
- sites of injury: peripheral nerves, spinal cord (posterior and lateral columns), cerebrum
- **clinical manifestation:** numbness and paresthesia in the extremities (the earliest neurological manifestation), glove-stocking peripheral neuropathy, difficulty in determining position and vibration sense, an increase in deep tendon reflex, weakness, ataxia; disturbances of mentation (from mild irritability and forgetfulness to severe dementia and frank psychosis)

Neurologic disease may occur in patients with a normal hematologic parameters

THERAPY WITH VITAMIN B_{12}

- initially, 1000μg/24h i.m. three times a week for two weeks
- to maintain a normal concentration of vit. B_{12} in plasma - i.m. 100 μg every 4 weeks or 1000 μg every 3 months
- if neurological abnormalities are present vitamin B_{12} injections should be given every 1-2 weeks for 6 months before switching to monthly injections

2. Folic acid deficiency anemia

CAUSES OF FOLIC ACID DEFICIENCY ANEMIA

Inadequate intake – unbalanced diet (common in alcoholics, teenagers, some infants**)**

Increased requirement:

a. pregnancy
b. infancy
c. increased hematopoesis (chronic hemolytic anemia)
d. chronic exfoliative skin disorders
e. hemodialysis

Malabsorption:

a. tropical sprue
b. nontropical sprue
c. **drugs: *phenytoin, barbiturates, ethanol***

Impaired metabolism:

a. **inhibitors of dihydrofolate reductase**: *methotrexate, pyrimethamine, triamterene, etc*
b. alcoholrare enzyme deficiencies: dihydrofolate reductase, others

General principles of therapy

1. prophylactic administration of folic acid.
   * pregnancy - a multivitamin preparation that contains 400 to 500μg of folic acid.
   * patient with a disease state with high cell turnover - one or two 1-mg tablets of folic acid.
   * women with a previous pregnancy resulting in a child with a neural tube malformation - 4 mg of folic acid per day
   * patients treated with metotrexate
2. Standard therapy – 1 (5) mg/day orally (reticulocytosis in 4-6 days)

Special clinical situations: megaloblastosis caused by:

- anticonvulsant therapy – folinic acid 1mg/day
- chronic pyrimethamine therapy – folinic acid 1-5mg/day (without blocking the antimalarial effect of pyrimethamine)
- methotrexate – folinic acid – severe anemia equivalent dose of folinic acid i.m. (milligram for milligram)
- methotrexate used in small doses (therapy of rheumatoid arthritis) – 5-15mg/week of folic acid 24h after the dose of methotrexate

Untoward effects

Folic acid in large doses may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone and increase the frequency of seizures in susceptible children.

Erythropoietin (EPO)

Mechanism of action: activation of specific receptors on erythroid progenitor cells in the bone marrow, stimulation of erythroid proliferation and differentiation

Indications

- anemia in patients with chronic renal failure
- therapy with AZT
- anemia after intensive chemotherapy
- secondary anemia in patients with bone marrow disorders
- anemia of prematurity

Therapy:

- Htc CONTROL – 2x/week; target level 30%; Hb target level – 10g/dl
- typically used dose – 50-100j.m./kg 3x/week sc
- supplementation with IRON (iv)

Side effects:

- hypertension,
- thrombotic complications,
- allergic reactions

Preparations:

Epoetin alfa – 3 x week sc

Darbapoetin alfa – differ from rhEPO by addition of 2 carbohydrate chains decreased clearance, increased half-time (3x) - 1 x week sc

G-SCF – Granylocyte Colony Stimulating Factor; Filgrastim

- **s**timulates CFU (colony forming unit) to neutrophil production
- enhances phagocytosis and cytotoxic activities of neutrophiles

Indications:
*****autologous bone marrow transplantation
*intensive chemotherapy
*congenital neutropenia
*neutropenia following AZT administration

ADVERSE REACTIONS
- bone pain,
- local skin reactions
- splenomegaly (long-term therapy)
- marked granulocytosis (100,000 ul – long-term therapy

PEGFILGRASTIM
Pegylation of filgrastim = ↑ in molecular size = no renal clearance =
↑ In half-life (3.5h → 42h)

GM-SCF – Granylocyte/Macrophage Colony Stimulating Factor; sargramostim
- increase neutrophil and monocyte production
- enhance migration, phagocytosis of neutrophils, monocytes
- and eosynophils

SIDE EFFECTS
- bone pain, malaise, flulike symptoms, fever
- diarrhea, dyspnea, rash
- prolonged administration – capillary leak syndrome (peripheral edema,
- pleural or pericardial effusions

Interleukin-11;oprelvekin
- stimulation of the growth of primitive megakaryocytic progenitors
- increase in the number of peripheral platelets and neutrophils

Indications:
thrombocytopenia – prevention and therapy
Side effects:
- fatigue, headaches, dizziness
- cardiovascular effects – fluid retention, anemia (hemodilution),
- dyspnea, transient atrial arrhytmias

Romiplostim
new therapeutic; „peptibody" = peptide + antibody fragment
Romiplostim = Fc component of human antibody + peptide that stimulates the thrombopoietin receptor
sc 1/week
Indications:
patients with idiopathic thrombocytopenia purpura
Toxicity:
headache

Eltrombopag
Orally active agonist of the thrombopoietin receptor
Indications:
patients with severe idiopathic thrombocytopenia purpura – second-line therapy
Toxicity:
Hepatotoxicity, hemorrhage