HAEMATINICS

- Substances required for blood formation
- They include Iron, Vitamin B_{12}, Folic Acid, Riboflavin, Pyridoxine, Copper, Erythropoietin, Zinc, Cobalt

IRON PREPARATIONS

- Iron absorption is increased by acids (ascorbic acid, amino acids) and decreased by alkalies, phosphates, phytates, tetracyclines, food
- *Richest Source:* dry fruits, egg yolk, jaggery
- *Poorest:* milk
- Ferrous iron better absorbed than ferric
- Requirement increases during pregnancy
- Total iron present in an average adult is 2.5–5 g

Uses

- Iron deficiency anaemia – nutritional deficiency, worm infestation, during pregnancy

Oral Iron Preparations

- Ferrous sulphate (cheapest, easily available) → 20% iron
- Ferrous gluconate, ferrous fumarate, colloidal ferric hydroxide, ferrous succinate, iron choline citrate, iron calcium complex, ferric ammonium citrate (scale iron), iron hydroxyl polymaltose
- Rise of Hb level of blood by 0.5-1 g/dl/week is considered adequate response to iron therapy
- Treatment with oral iron should be continued for 3-6 months. This will correct the anaemia and replenish iron stores

Adverse Effects

- Metallic taste, staining of teeth, epigastric distress, constipation (common), also can cause diarrhoea

Parenteral Iron Preparations

- Iron Dextran (IM/IV)
- Iron sorbitol-citric acid (only IM)
- Iron requirement in mg: 4.4 x body weight (Kg) × Hb deficiency (gm%)
- Allergic reactions very high, always test dose given
- Technique of iron injecting (IM) – Z-tract technique in gluteus maximus (done to avoid pigmentation of skin)

Indications

- Oral iron not tolerated due to bowel upset
- Failure to absorb oral iron
- Non compliance of patient
- Severe deficiency with bleeding
- Along with erythropoietin

Adverse Effects

- Pain on IM injection, pigmentation, sterile abscess, fever, headache, joint pain, palpitations, flushing, lymph node enlargement

Iron Dextran

- IM/IV use
- High molecular weight
- Does not bind to transferrin
- Not excreted
- High local tissue binding capacity

Iron Sorbitol Citric Acid Complex

- IM
- Low molecular weight
- Binds to transferrin
- Excreted in urine
- Local tissue binding absent

Acute Iron Poisoning

- Common in children (10-20 tablets can cause toxicity)
- Haematemesis, abdominal cramps, cyanosis, dehydration, acidosis, CV collapse

Treatment

- Gastric lavage with $NaHCO_3$, milk or egg yolk given to complex iron, supportive measures
- IV/IM, Desferrioxamine specific antidote (orally – Deferiprone, Deferasirox)
- BAL – contraindicated in Fe poisoning (because the complex again is toxic)

VITAMIN B_{12} PREPARATION

- Cyanocobalamin, Hydroxocobalamin, Methylcobalamin
- Vitamin B_{12} – extrinsic factor requires Intrinsic Factor (IF) of Castle (parietal cells) for absorption
- Deficiency of IF → leads to Pernicious anaemia
- Pernicious anaemia → vitamin B_{12} always given as injection (never orally)
- Daily requirement: 1-3µg, pregnancy 3-5µg
- Methylcobalamin – preferred for neurological defects

- Hydroxocobalamin – preferred for injection due to better retention
- Vitamin B_{12} injection always given after test dose
- Besides Vitamin B_{12} deficiency – Hydroxocobalamin tried in tobacco amblyopia
- Deficiency occurs due to
  1. Addisonian pernicious anaemia
  2. Chronic gastritis, gastric carcinoma, gastrectomy
  3. Malabsorption
  4. Blind loop syndrome/D. latum infestation
  5. Nutritional deficiency
  6. Drug induced – Metformin, Barbiturates

Clinical Features

- Megaloblastic anaemia – weakness, fatigue, glossitis, diarrhoea, peripheral neuritis, poor memory, spinal cord degeneration

Function

- Conversion of homocystiene to methionine, malonic acid to succinic acid, methionine to s-adenosyl methionine

FOLIC ACID (PTEROYL GLUTAMIC ACID)

- Also called Will's factor
- Richly present in green leafy vegetables
- ***Function:*** generation of thymidylate, conversion of homocystiene to methionine, purine synthesis
- ***Deficiency:*** nutritional deficiency, malabsorption syndrome, chronic alcoholism, drug induced like anti epileptic therapy, oral contraceptives.
- ***Clinical Features:*** anaemia, glossitis, diarrhoea, neural tube defects, weight loss, general debility
- Folic acid usually given orally
- Folinic acid (also called N-formyl THFA) – (calcium leucovorin/citrovorum factor rescue) used for Methotrexate toxicity

ERYTHROPOIETIN

- Sialoglycoprotein, produced by Peritubular cells of kidney
- Stimulate colony forming cells of erythroid series
- Induces Hb formation
- Releases reticulocytes in circulation
- Obtained by recombinant DNA technology called as Darbopoietin α – given SC/IV 3 times a week
- ***Uses:*** anaemia in AIDS, chronic renal failure, cancer chemotherapy
- ***Adverse Effects:*** increased blood viscosity → clot formation, hypertension, flu like syndrome, seizures

COAGULANTS

- These are substances which promote coagulation, and are indicated in haemorrhagic states

CLASSIFICATION

1. Vitamin K
   - K_1 (plants) – Phytonadione (Phylloquinone)
   - K_2 (animals) – Menaquinone
   - K_3 (synthetic) – Menadiones, Acetamenaphthone
2. Fibrinogen
3. Anti-haemophilic factors
4. Desmopressin
5. Adrenochrome monosemicarbazone
6. Rutin
7. Ethamsylate

VITAMIN K

- Fat soluble
- Cofactor for II, VII, IX, X – clotting factors
- Required for γ- carboxylation of glutamate residues of above clotting factors which makes the CF active so that they bind to Ca^{2+} and get bound to phospholipid surfaces

Causes of Deficiency

- Malabsorption, liver diseases, obstructive jaundice, prolonged antimicrobial therapy

Symptoms

- Bleeding tendencies (first haematuria)

Uses

1. Over dosage of anticoagulant (Warfarin), Phytonadione (K1) - drug of choice
2. Used in newborn (there is always vitamin K deficiency, CF deficiency)
3. Liver diseases, obstructive jaundice, prolonged salicylate therapy

Adverse Effects

- Rapid IV injection causes breathlessness, chest pain, flushing, decrease BP

- Menadiones – causes haemolysis in G6PD deficient individuals and neonates
- It also can cause kernicterus in newborns, hence contraindicated in newborns

FIBRINOGEN

- To control bleeding in haemophilia, AHG deficiency, acute afibrogenemia

DESMOPRESSIN

- Releases factor VIII, VWF → used in haemophilia, von Willebrand diseases

RUTIN

- Plant glycoside

ETHAMSYLATE

- Controls capillary bleeding, improve capillary wall stability, also exerts antihyaluronidase action

ANTICOAGULANTS

- These are drugs used to reduce the coagulability of blood

Used in Vivo	Used in Vitro
1. ***Parenteral*** Heparin, Low Molecular Weight (LMW) Heparin, Danaparoid, Lepirudin, Ancrod 2. ***Oral*** i. *Coumarin derivatives:* Bis hydroxy Coumarin (Dicoumarol), Warfarin, Acenocoumarol, Ethyl Biscoum Acetate ii. *Indandione derivatives:* Phenindione (not used now due to toxicity)	1. Heparin (150U → for 100ml of blood) 2. Sodium citrate 3. Sodium oxalate 4. Edetate

HEPARIN

- First discovered by Mc Lean (medical student) that liver contains an anticoagulant
- Mucopolysaccharide – MW 10,000 – 20,000 posses' strong electro negative charge
- Heparin acts by activating Antithrombin III (AT III) which then binds CF (II, VII, IX, X, XI, XII, XIII) and inactivates them
- Predominantly affects intrinsic pathway
- Monitoring done by – aPTT
- High doses also has mild antiplatelet activity
- Also clears turbid plasma (Lipaemia clearing)
- Fastest acting anticoagulant, not absorbed orally
- Given IV/SC (not IM → cause haematoma)
- Heparin should not be mixed with antibiotics, steroids
- Commercial sources: Ox lung, Pig intestinal mucosa
- Pregnant females receiving heparin therapy should be supplemented with calcium (to prevent osteoporosis)

Mechanism

- Heparin activates Anti thrombin III (AT-III) by 2 mechanisms
  1. Long heparin molecule provides scaffolding (support) for both clotting factors and AT-III to get bound and interact with each other
  2. It also induces conformational change in AT-III molecule to expose its interactive sites
- For inhibition of factor II (Prothrombin), it requires both the mechanisms, but for X inhibition, only (b) mechanism is sufficient. Hence LMW Heparin, which acts only through (b) mechanism, can not inhibit factor II, but inhibits only X. LMW Heparin, can not provide scaffolding due to its smaller size compared to Heparin

Adverse Effects

- Bleeding, thrombocytopenia, transient alopecia, osteoporosis, hypersensitivity
- HIT (Heparin Induced Thrombocytopenia) syndrome occurs due to formation antibodies against complexes of heparin with platelet factor 4, that can result in paradoxical thrombosis. Treatment for it is direct thrombin inhibitors like Lepirudin and bivalirudin. Fondaparinux can also be used.

Contraindications

- Bleeding disorders, SABE, hypertension, bleeding peptic ulcer, ocular & neurosurgery, along with aspirin

LMW HEPARIN

- Molecular weight: 3000 - 7000
- Ex: Dalteparin, Enoxaparin, Nadroparin, Reviparin, Pamparin, Ardeparin, Fondaparinux

- Better subcutaneous bioavailability
- Longer t ½
- *Heparin antagonist* – protamine sulphate obtained from sperms of fish, highly basic substance, releases histamine and causes severe allergic reactions
- In absence of heparin, it also has anticoagulant property

Mechanism

- Induces conformational changes on AT III to expose its interactive sites
- Predominantly inhibits only Xa (little effect on IIa)
- Hence no requirement of strict lab monitoring of aPPT, PT

DANAPAROID

- Obtained from pig gut mucosa, used for heparin induced thrombocytopenia

LEPIRUDIN

- Recombinant preparation of Hirudin (direct thrombin inhibition) used for heparin induced thrombocytopenia

HIRUDIN

- Obtained from salivary gland of leech

ANCROD

- Obtained from Malayan pit viper venom – degrades fibrinogen

WARFARIN

- Was also used as rat poison in beginning
- Acts only in Vivo (not in Vitro)
- Acts as vitamin K antagonist
- Prevents generation of vitamin K hydroquinone required for activation of II, VII, IX, X
- Slow onset of action; takes 1-3 days for action
- Used only for maintenance
- High plasma protein binding
- Teratogenic

Adverse Effects

- Bleeding, alopecia, dermatitis, diarrhoea

Antidote

- Vitamin K (Phytonadione)

During Pregnancy

- If prescribed, causes skeletal abnormalities, hypoplasia of nose, eye, sockets, hand bones, growth retardation, foetal haemorrhage
- Warfarin →lot of drug interaction
- Heparin → safe in pregnancy (does not cross placenta)
- Warfarin → dose monitored by PT (Prothrombin Time)

Uses

- Deep vein thrombosis, pulmonary embolism, acute MI, unstable angina, RHD with atrial fibrillation, cerebral thrombosis, vascular surgery, haemodialysis

FIBRINOLYTICS/THROMBOLYTICS

- These are drugs used to lyse thrombi/ clot to recanalize occluded blood vessels (mainly coronary artery)
- Important ones are
  1. Streptokinase
  2. Alteplase
  3. Urokinase
  4. Reteplase
  5. Tenecteplase
  6. Anistreplase
- Reteplase & Tenecteplase are known as bolus fibrinolytics

Mechanism of Action

- Combines with circulating plasminogen to form an activator complex which then causes limited proteolysis of other plasminogen molecules to plasmin

Uses

1. Acute myocardial infarction
2. Deep vein thrombosis
3. Pulmonary embolism
4. Peripheral arterial occlusion
5. Stroke

ANTIFIBRINOLYTICS

- These are drugs which inhibit plasminogen activation and dissolution of clot, and are used to check fibrinolysis associated bleeding

- They include
  1. EACA-Epsilon Amino Caproic Acid
  2. Tranexamic acid
  3. Aprotinin

Uses

1. Overdose of fibrinolytics
2. After cardio-pulmonary bypass surgery
3. After tonsillectomy, prostatic surgery, tooth extraction in haemophiliacs
4. Menorrhagia, especially due to IUCD
5. Recurrent epistaxis, ocular trauma, bleeding peptic ulcer

Adverse Effects

- Nausea and diarrhoea
- Headache
- Giddiness
- Thrombophlebitis of injected vein
- Arrhythmias
- Hypotension
- Intravascular thrombi (EACA)

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