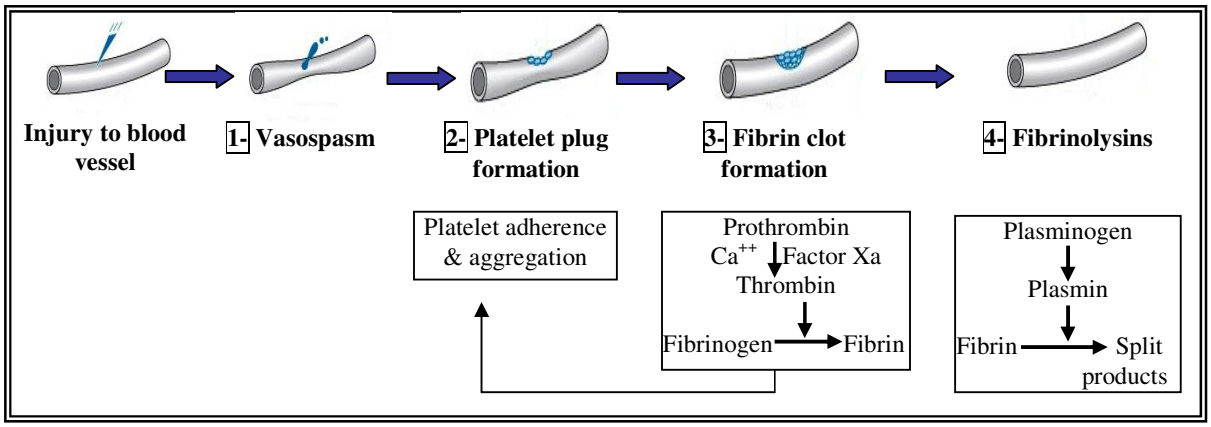
ANTITHROMBOTIC DRUGS



1- ***Antiplatelets:*** for *prophylaxis* of thromboembolic disease.
2- ***Anticoagulants:*** for *ttt* of thromboembolic disease.
3- ***Fibrinolytics:*** for *rapid dissolution* of thromboemboli

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(1) Anticoagulants

Classification:

1) In vitro only anticoagulants:

- Substances which remove ionic calcium
- Used in laboratory blood samples
- They include:
  - **a- Calcium precipitants:** e.g.: Na or K oxalate
  - **b- Diminished ionized calcium:**
    e.g.: Na citrate (in blood samples and banks) and EDTA.

2) In vivo anticoagulants:

1- Direct acting (Thrombin inhibitors):

a- Indirect thrombin inhibitors:
- Antithrombin III activator: ***Heparins***
  - Unfructionated Heparin (UFH)
  - Low molecular weight Heparin (LMWH)
- Selective factor Xa inhibitor: *Fondaparinux*

b- Direct thrombin inhibitors:
- *Hirudin*
- Recombinant hirudin (*Lepirudin – Bivalirudin*)
- Synthetic: (*Argatroban – Ximelagatran*)

2- Indirect acting (Vit. K antagonists):

a. Coumarins: *Dicoumarol – **Warfarin***
b. Indanedione: *Phenindion (Dindivan) - Diphenadion*

N.B: Oral anticoagulants include: vit. K antagonists & Ximelagatran

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N.B: Ancrod: extract of viper venom that deplete circulating fibrinogen

Comparison between Heparin and Warfarin

	Heparin* **(Unfractionated heparin)**	**Warfarin**
Source	- Naturally found with histamine in mast cells in liver & lung	- Coumarin** is natural - Warfarin*** is Synthetic
Chemistry:	- Mucopolysaccharide strongly acidic with strong *electronegative charge*	- Coumarine derivative
Kinetics:	- Parenteraly (I.V.) or (S.C) never I.M (haematoma) - Metabolized in liver and tissues (by heparinase enzyme) - Not cross the placenta & Not secreted in milk (Allowed in pregnancy & lactation) - Excreted in urine	- Given orally, bound to plasma protein - Metabolized in liver - Cross the placenta & secreted in milk (Not Allowed in pregnancy & lactation) - Excreted in urine & milk
Onset & Duration:	- Immediate after I.V. - Short duration [4 hr after I.V.]	- Delayed onset 1-2 days - Long duration [4-7 days]
Actions:	**1) Anticoagulant** in vivo& vitro Potentiating the action of *antithrombin III* which neutralizes & inhibit many clotting factors **2) Lipaemea clearing action** due to activation of lipoprotein lipase enz.	**1) Anticoagulant** in vivo only ↓Vit.K reductase enz. ➔↓ Conversion of vit.K epoxide into the active form required for synthesis of coagulation factors: II (prothrombin),VII, IX, X & anticoagulant proteins: C & S **2) Rodenticide** 
Dose:	* Initially: 70-100 U / kg * Maintenance: infusion 15-25 U/kg / h	- Initially 10 mg/day 3 doses - Maintenance 4-5 mg / day
Control of the dose:	**(1) Coagulation time:** Prolonged 2-2.5 times (normally 5-7 min.) **(2) Partial thromboplastin time (PTT):** Prolonged 2-2.5 times (normally 30-40 sec.)	**(1)** Prothrombin time (PT): Prolonged to 2-2.5 times (normally 12-15 seconds) ***NB:*** *International Normalized Ratio (INR)* is more accurate $= \frac{\text{PT of patient}}{\text{PT of normal}}$
Uses	**1) Treatment of thromboembolic disease:** - Myocardial infarction - Pulmonary embolism - Venous & Cerebral thrombosis **2) Prophylactic:** of venous thrombosis & Pulmonary embolism [not effective on arterial thrombosis] **3) Prevent blood clotting** During transfusion (heparin) **4) In hyperlipidemia** (heparin)	

*Heparin: was discovered by a medical student in 1916 in a physiological research to study clotting substances in the body. To his surprise he found that extract from the liver retarded the clotting process, and hence its name " hepa"

**Coumarin: was discovered as an anticoagulant substance formed in spoiled sweet clover silage which caused hemorrhage in cattle

***Warfarin: the name is derived from the patent holder, **W**isconsin **A**lumni **R**esearch **F**oundation & "arin" from coum**arin**

Side effects	1) *Hemorrhage* *2) Hypersensitivity* 3) Hyperkalemia (antagonize aldosterone) 4) Hair loss (transient alopecia) 5) Osteoporosis 6)* ***Thrombocytopenia* &** **paradoxical thrombosis ***	1) *Hemorrhage* *2) Hypersensitivity* 3) Anorexia, nausea & vomiting 4) Teratogenicity (Skeletal abnormalities & hypoplastic nose) 5) Skin necrosis (rare): due to ↓ of synthesis of anticoagulants C & S
Antidote	1) ***Protamine sulphate* I.V.:** 1 mg for 100 U (1ml) heparin (Strongly electro- positive charged) 2) Fresh blood transfusion	1) ***Vitamin K_1***: 50 mg I.V 2) Fresh blood transfusion
Contra-indication	1) Allergy to the drug 2) Liver & kidney disease 3) Anticoagulant not desired: - Active T.B - Subacute bacterial endocarditis - Peptic ulcer & ulcerative colitis 4) Bleeding conditions: - Bleeding tendency (haemophilia) - Head injury - Threatened abortion - Visceral carcinoma	

Drug, food & disease interactions of Oral anti-coagulants

(1) ↑ Anti coagulant effect may be due to:

1. Kinetic interaction:
   - a- Displacement from plasma proteins by: Aspirin- Phenylbutazone- Indomethacin- Clofibrate- Sulphonamide- Sulphinpyrazone
   - b- HME inhibitor as Cimitidine- Chloramphenicol- Allopurinol
2. Dynamic interaction:
   - a- ↓ vit K: - ↓ synthesis by broad spectrum antibiotics, e.g.: Tetracycline
     - ↓ absorption by liquid paraffin
   - b- ↓ Platelet aggregation & function as
     - Aspirin S.D
     - Cephalosporins (third generation) [Also have anti vit K affect]
   - c- Androgen [due to ↑ turnover of clotting factors)
3. Pathological:. Liver disease, hyperthroidism

(2) ↓ anti coagulant effect may be due to:

1. Kinetic interaction:
   - ↓ Absorption as cholestyramine
   - ↑ Metabolism by HME inducers as phenobarbitone- rifampicin- griseofulvin
2. Dynamic interaction:
   - ↑ Clotting factors by estrogen
   - vit.K (including food rich in vit. K as green, leafy vegetables)
3. Pathological: Hypothyroidism & hereditary resistance

N.B: Choice of anticoagulant:

- Begin therapy with heparin and oral anticoagulant together then after 4-5 days withdraw heparin and maintain on oral anticoagulant for 3 months
- Heparin is used for emergency & during pregnancy

***N.B.: Heparin induced Thrombocytopenia:**

- Types:

- *Type I:* Mild - Non immunologic induction of platelet aggregation
- *Type II:* Severe - Immunological induced platelet aggregation due to formation of immune complexes

- **May cause** paradoxical thrombosis
- **Management:** Stop heparin & replace by another anticoagulant as direct thrombin inhibitors

LMW heparins

- Examples: *Enoxaparin – Dalteparin – Rivaparin - Danaproid*

- Mechanism of action:

potentiate the effect of antithrombin III selectively on activated factor X & have less effect on other coagulation factors.

- Differences versus Unfractionated heparin:

- They have *equal efficacy* to UFH
- *increased S.C bioavailability*
- *Less frequent dose administration*
- *Can be given without laboratory monitoring*

Direct thrombin inhibitors

- Uses:

As alternative to heparin for patients *with heparin induced thrombocytopenia*

- Differences versus Heparin:

They produce *a more predictable anticoagulant response* than UFH because they do not bind to plasma proteins & are not neutralized by platelet factor 4, a heparin-binding protein released from activated platelets.

- Include:

- *Hirudin*
- Recombinant hirudin (*Lepirudin – Bivalirudin*)
- Synthetic: (*Argatroban – Ximelagatran*)

N.B.: *Ximelagatran* is the only one of this group which is given *orally*, while others are given IV

N.B.: Drotrecogin Alfa ***(Xigris)*****:** is a recombinant form of protein C that *inhibits coagulation* by proteolytic inactivation of factors Va & VIIIa. It has also *anti-inflammatory* effect & used as IV infusion in cases of severe sepsis

2) Anti-Platelet Agents

Uses:

1- Prevention & treatment of occlusive cardiovascular disease (eg.: Angina)
2- Maintain vascular grafts & arterial patency
3- Adjuvant to thrombolytics during myocardial infarction

Classification &Mechanisms

(1) Drugs acting on Arachidonic acid metabolism:

1- ↓ Thromboxane A_2 synthesis

1. Aspirin Small Dose (75-150 mg): selective ↓ of platelet thromboxane
2. Dazoxiben: as aspirin Small dose
3. Sulphinpyrazone: ↓ COX
4. Fish oil: abnormal thromboxanes

2- Prostacyclin analogue:

➔ Epoprostenol but very short t ½

(2) Drugs that ↑ c. AMP & c.GMP:

1- ↑ c. AMP

1. Dipyridamol: ↓ PDE enz ➔ ↑ c. AMP
2. Pentoxiphylline: as Dipyridamol

2- ↑ c. GMP

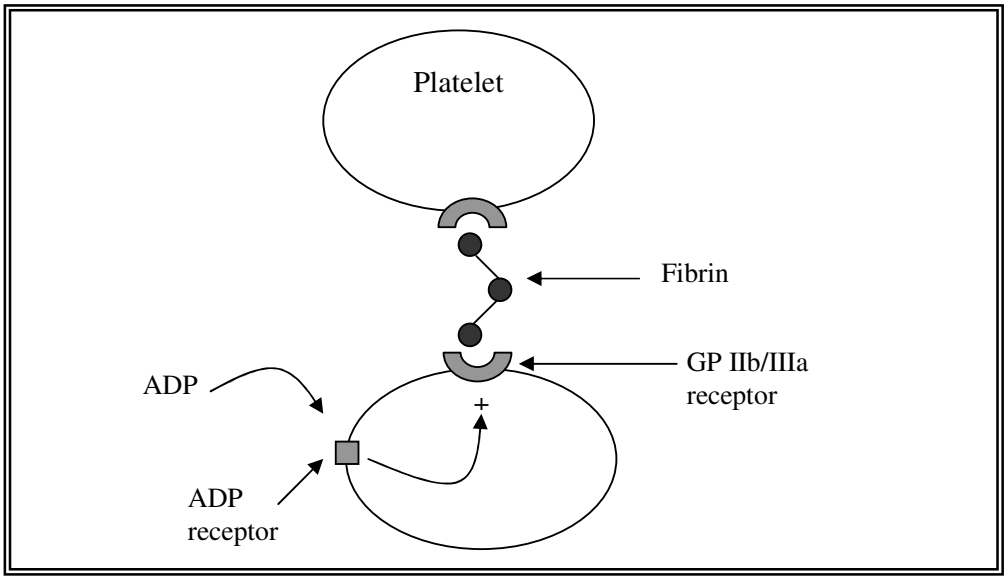
Nitrates & Nitroprusside ➔ release (NO) ➔ ↑ G.C ➔ ↑ c.GMP

(3) Drugs acting on platelet receptors:

1- Block ADP receptors [block ADP dependent activation of GP IIb/IIIa receptors]As: Ticlopidine & Clopidogrel

2- Block GP IIb /IIIa receptors:

Abciximab – Tirofiban – Integrelin – Eptifibatide



3) Fibrinolytics (Thrombolytics)

- Uses:

They produce dissolution of blood clot (Thrombosis or Embolism) of **recent onset** (as in myocardial infarction or peripheral arterial thrombosis)

- They include:

1) Streptokinase (Obtained from streptococci)
2) Urokinase
3) Tissue plasminogen activator [Al**teplase**]
4) Re**teplase** - Tenec**teplase**
4) Anistreplase [APSAC]

- Mechanism of action: by activation of plasminogen

Plasminogen ⟶ Plasmin (fibrinolysin) ⟶ Dissolve fibrin

NB.:

	Streptokinase:	***Alteplase:***
Mechanism	bind to plasminogen to form a complex & this complex converts Plasminogen ➔ Plasmin (fibrinolysin)	activate plasminogen that is bound to fibrin (it is fibrin selective)
$t_{1/2}$	< 30 min.	< 5 min.
Dose	1.5 million IU over 30-60 min.	100 mg IV (10 mg initial bolus & the remaining IV infusion over 90 min.)

- Side effects:

1- Bleeding (The most important & most common)
2- Allergy (especially with Streptokinase)
3- Fever

- Contraindications:

1- Persistent hypertension
2- Aortic dissection
3- Trauma
4- Pregnancy
5- History of recent: surgery or cerbrovascular stroke
6- Active GIT bleeding

NB.: Antifibrinolysin:

Aminocaproeic acid & Tranexamic acid

Coagulants [Control of bleeding]

Local haemostatics (styptics)

1) Local coagulants

1. Human fibrin (sponge)
2. Human fibrinogen
3. Human thrombin (powder)
4. Human thromboplastin (powder)
5. Oxidized cellulose (oxycel): mechanical blockage (artificial clot)
6. Sponge gelatin

2) V.C Adr. & noradr. In epistaxis

3) Astringent tannic acid, alum➔ precipitate blood proteins

4) Physical method: [Pressure & cold]

Systemic coagulants:

1) Vitamin K:

* Used to correct bleeding from hypoprothrombinaemia that may result from:
  1. ↓ Synthesis of vit.K by intestinal flora ➔ oral antibiotics
  2. ↓ Absorption of vit. K ➔
     - Liquid paraffin - Obstructive jaundice - Malabsorption
  3. ↓ Hepatic utilization of vit.K ➔ hepatocellular damage – newborn
  4. Drug induced hypoprothrombenemia ➔
     - Oral anti coagulants - Aspirin L.D.

* Sources & Preparations

1. Natural:

- Vit. K_1 (phytonadione) orally or I.M.
  It is found in food – concentrated in liver
- Vit. K_2 (menaquinone):
  formed by intestinal bacteria – concentrated in bone & blood vessels

2. Synthetic (more toxic):
Menadione & Menadione di-phosphate ➔ I.M – S.C

2) Vit. C & vit. P (Rutin) ➔ used to treat capillary fragility as in bleeding gums & scurvy

3) Antihaemophilic globulin (Factor VIII): I.V to treat bleeding from haemophilia

4) Antidote for drug toxicity causing bleeding:

1- If due to thrombolytic drugs ➔ Aminocaproic acid & Tranexamic acid
2- If due to heparin ➔ Protamine sulphate
3- If due to Oral anticoagulants eg.: Warfarin ➔ vit.K

5) Thromboplastin (coagulin): I.M

6) Fresh blood transfusion:

NB: Sclerosing agents

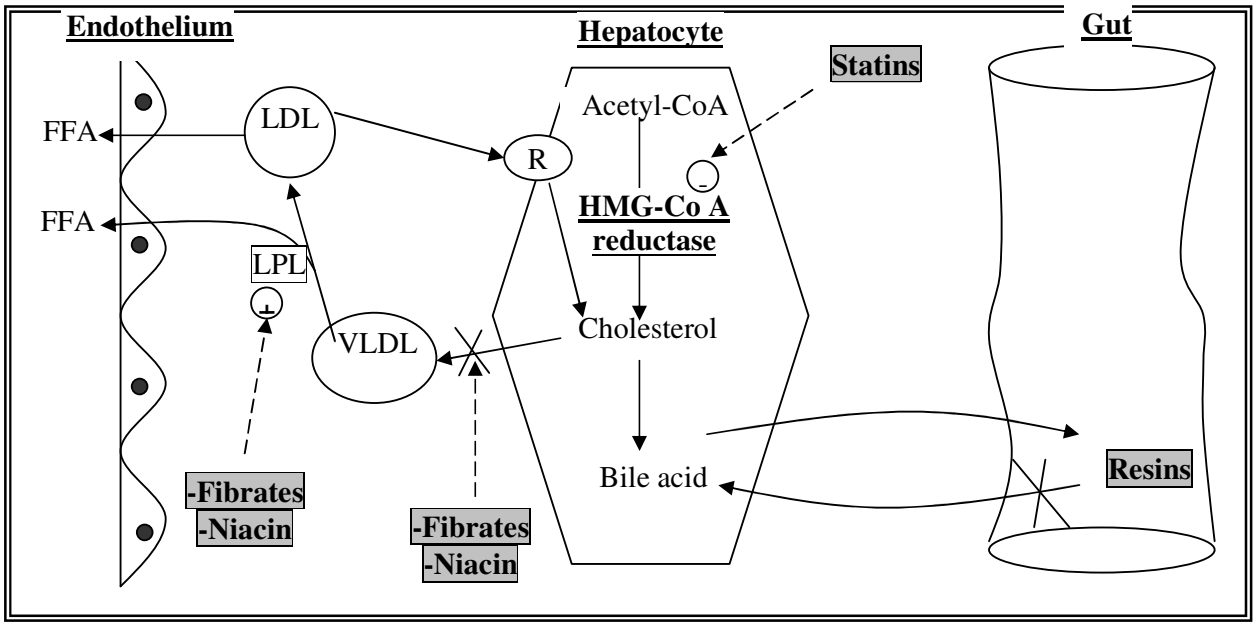
Irritant substances injected in veins of legs and piles to initiate venous thrombosis

1) Sodium morhuate 2) Sylnsol 3) Sorietin

Hyperlipoprotinemia

Lipoproteins are classified to:

1) Chylomicron
2) VLDL: [Containing Triglyceride > Cholesterol ester] transporting lipids to peripheral tissue
3) LDL: [Containing mainly cholesterol ester]
4) HDL: transport cholesterol away from peripheral tissues to liver [protective]



Drugs management of hyperlipidemia

	1) Statins HMG – Co A reductase inhibitors	2)Fibrates	3)Resins
Examples	- Atorvastatin - Pravastatin - Lovastatin - Simvastatin - Fluvastatin	- Clofibrate - Etofibrate - Fenofibrate - Gemfibrozil	- **C**holestyramine - **C**olestipol
Mechanism	they ↓ HMG – Co A reductase enz [rate limiting enz] ➔ ↓ cholesterol synthesis ➔ compensatory ↑ in LDL receptors on hepateocytes ➔ ↓ LDL & cholesterol	↓ Triglycerides through : 1. ↑ Lipoprotein lipase enz. 2. ↓ Hepatic synthesis of T.G & VLDL	they bind with bile acid ➔ 1- ↓ Absorption of cholesterol 2- ↓ Absorption of bile ➔ ↑ catabolism of cholesterol into bile acids ➔compensatory ↑ in LDL receptors ➔ ↓ LDL &Cholester.

Side effects:	*1. Hepatotoxic ➔ ↑ serum tansaminases* *2. Myopathy & myositis ➔ ↑ serum creatine kinase* *3. Contra indicated in pregnancy & lactation*	*1. Hepatotoxic ➔ ↑ serum transaminases* *2. Myopathy & myositis ➔ ↑ serum creatine kinase* *3. Contraindicated in pregnancy & lactation* 4. Cholesterol gall stones & cholecystitis 5. Displace other drugs from plasma proteins	1. **C**onstipation 2. **C**holesterol gall stones & cholecystitis 3.↓ Absorption of vit. K & other drugs e.g.: digoxin & warfarin.

(4) Niacin: [nicotinic acid]

2. **Mechanism:** As Fibrates
3. **Side effects**:
    1. ***Pruritis & flushing*** due to release of PGs. Avoided by aspirin
    2. Hyperglycemia & hyperuricemia
    3. GIT disturbances

N.B Acipimox: as niacin with less side effects.

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5) Ezetimibe:

- It ↓ directly cholesterol absorption
- Metabolised in liver (not used in advanced liver disease)

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(6) Probucol:

4. **Mechanism**: anti oxidants & ↓ cholesterol synthesis
5. **Side effects**:
    1. GIT disturbances
    2. Fatal arrhythmia & long Q-T interval

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(7) Others:

1. Neomycin ➔ as resins ➔ ↓ cholesterol absorption
2. B-.Sitosterol ➔ as resins ➔ ↓ cholesterol absorption
3. D- thyroxin: ↑ catabolism of cholesterol into bile acids & compensatory ↑ in LDL receptors

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N.B: fish oil ➔ ↓ TG **but** ↑ cholesterol

N.B: *Alpha tocopherol [vit.E]:*

Has no effect on lipid level but it ↓ atheroma formation as it is a powerful antioxidant, & oxidation of LDL is essential for atheroma formation.

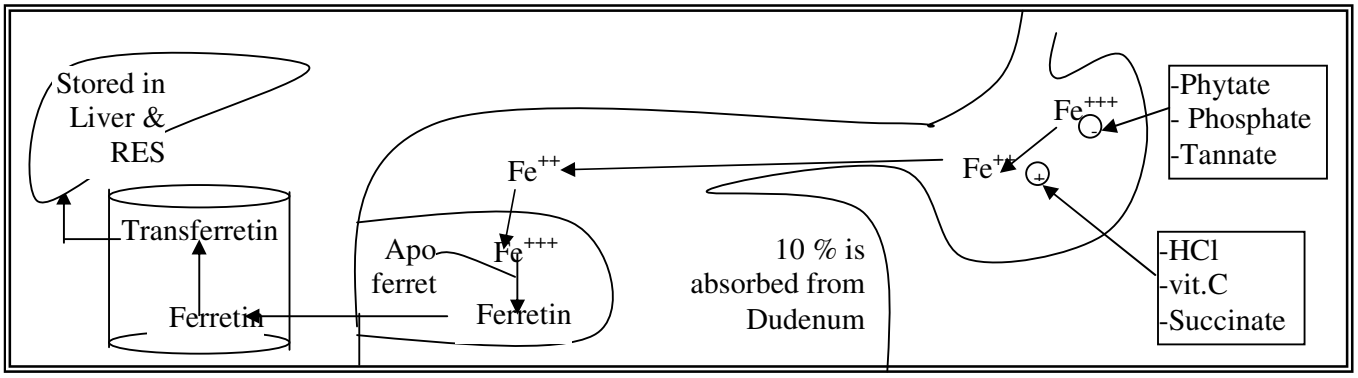
Antianaemic drugs

Types of anaemia

I- Deficiency anaemia. (Iron – B_{12} – folic acid)
II- Aplastic anaemia
III- Haemolytic anaemia

I - deficiency anemia

1- Iron



Preparations:

Oral preparation

Ferrous sulphate - Ferrous gluconate - Ferrous fumarate - Iron choline citrate

Parenteral preparation

1. Iron Dextran I.M, I.V.
2. Iron sorbitol citric acid complex I.M. ***only***

Side effects and toxicity:

Oral iron

- **Gastric irritation**, colicky pain, constipation or diarrhea & black stool
- **Acute toxicity** (usually, accidentally in children):

Manifestations:

- Vomiting, abdominal pain, haematemesis and black or bloody diarrhea
- Hypotension, collapse, coma, death in some cases

Treatment:

6. Gastric lavage with $NaHCO_3$ 1%
7. Iron chelating agents : **Deferoxamine** (desferal): given by stomach tube - I.M. or I.V. infusion
8. Symptomatic treatment (eg:fluids for dehydration & collapse)

Parenteral iron preparation

Local toxic effect:

- Pain at site of injection - Skin discoloration

Systemic toxic effect (Chronic toxicity = Haemosidrosis)

- Manifestations:
- Headache, malaise, convulsions, fever & fainting
- Nausea and vomiting - Muscle and joint pains, haemolysis
- Tachycardia & Hypotension - Bronchospasm

- Treatment:
  - Intermittent phlebotomy (every weak), provided that there is no anemia
  - Parentral Deferoxamine or Oral ***Deferasirox***

NB.: Iron is contraindicated in haemolytic anemia, unless haemoglobinuria is present
NB.: Both iron & tetracycline inhibit absorption of each other

2- Cyanocobalamine (vit. B_{12})
Extrinsic factor, Antipernicious anaemia factor

The manifestations of deficiency are Pernicious anemia:

1. Macrocytic hypochromic anaemia
2. Peripheral neuritis and subacute combined degeneration

N.B: the primary cause for pernicious anemia is absence of intrinsic factor required for absorption of vit B_{12} from terminal ileum
N.B: *Drugs that may inhibit absorption of vit. B_{12}:*
Neomycin – PAS (para-aminosalicylic acid) - Metformin

Uses:

1. Pernicious anemia and macrocytic anemia
2. Neuropathies
3. Hepatitis
4. Counteract catabolic action of cortisone

Preparations:

1. Cyanocobalamine : I.M. for life 1 mg
2. Hydroxocobalamine I.M. for pernicious anemia and cyanide poisoning

3- Folic acid

Fate:

1. By folic acid reductase ➔ tetrahydrofolic acid T.H.F.A. (active)
2. Both folic acid and B_{12} are closely interrelated

$$\text{Conj. Folic acid} \xrightarrow{B_{12}} \text{free folic acid} \xrightarrow{\text{vit. C, } B_{12}} \text{T.H.F.A.}$$

Uses:

1) Megalobastic anemia (nutritional and pregnancy)
2) Mal-Absorption Syndrome
3) With anticonvulsant drugs as phenobarb., primidone or phenytoin to correct associated marocytic anaemia.

N.B:
- In pernicious anaemia it must be given with vit. B_{12} otherwise neurological damage will proceed if folic a. is used alone
- Methotrexate (used in cancer therapy) is antifolic acid

II- Agranulocytosis / Aplastic anaemia

Causes:

1) **An**algesic ➔ pyrazolone eg.: (Dipyrone)
2) **An**tithyroid ➔ thiouracil
3) **An**tibacterial ➔ chloramphenicol and sulphonamide
4) **An**tiepileptic➔ Trimethadione
5) **An**tineoplastic drugs (Cytotoxic drugs)
6) Gold

The early manifestation of agranulocytosis is *sore throat*

Treatment:

1) Stop the cause
2) ***Blood transfusion***
3) Vit. B_{12} and folic acid, vit.C
4) Haemopoietic growth factors
5) Antimicrobial for infections

Met-hemoglobinaemia

It is the conversion of Fe^{++} of haemoglobin into Fe^{+++}

Causes :

1. Phenacetine
2. Nitrite
3. Sulphonamides
4. Primaquine

Treatment by:

1. Methylene blue
2. Vit. C "ascorbic acid"

Hematopoietic growth factors

Developed using recombinant DNA technique and include:

1. **Erythropoietin:** produced primarily by renal cortex, used mainly in treatment of anemia due to chronic renal failure. But can be used also in AIDS and in anemia of cancer therapy.
2. **Thrombopoietin** is a cytokine that increases platelet count when combined with other growth factors.
3. **Granulocyte / marcrophage colony- stimulating factor (GM-CSF):** used to stimulate myelopoiesis in AIDS, aplastic anemia and cancer chemotherapy.
4. **Granulocyte colony- stimulating factor (G-CSF)** is used to treat severe neutropenia following bone marrow transplantation or cancer chemotherapy.
5. **Interleukins** (IL 1, 3, 5, 6, 9, 11) act synergistically with stem cell factor (SCF), GM-CSF, G-CSF and erythropoietin.