PC
Pharmacology Concepts
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Drugs Used in Blood Disorders

Website

Videos

Pharmacology 2 | U2

HAEMATINICS : BLOOD FORMING AGENTS

The substance or agents, which are required in the formation of Blood, and are used for treatment of "Anaemias"

ANAEMIA :- Decreased Hb/RBCs contents

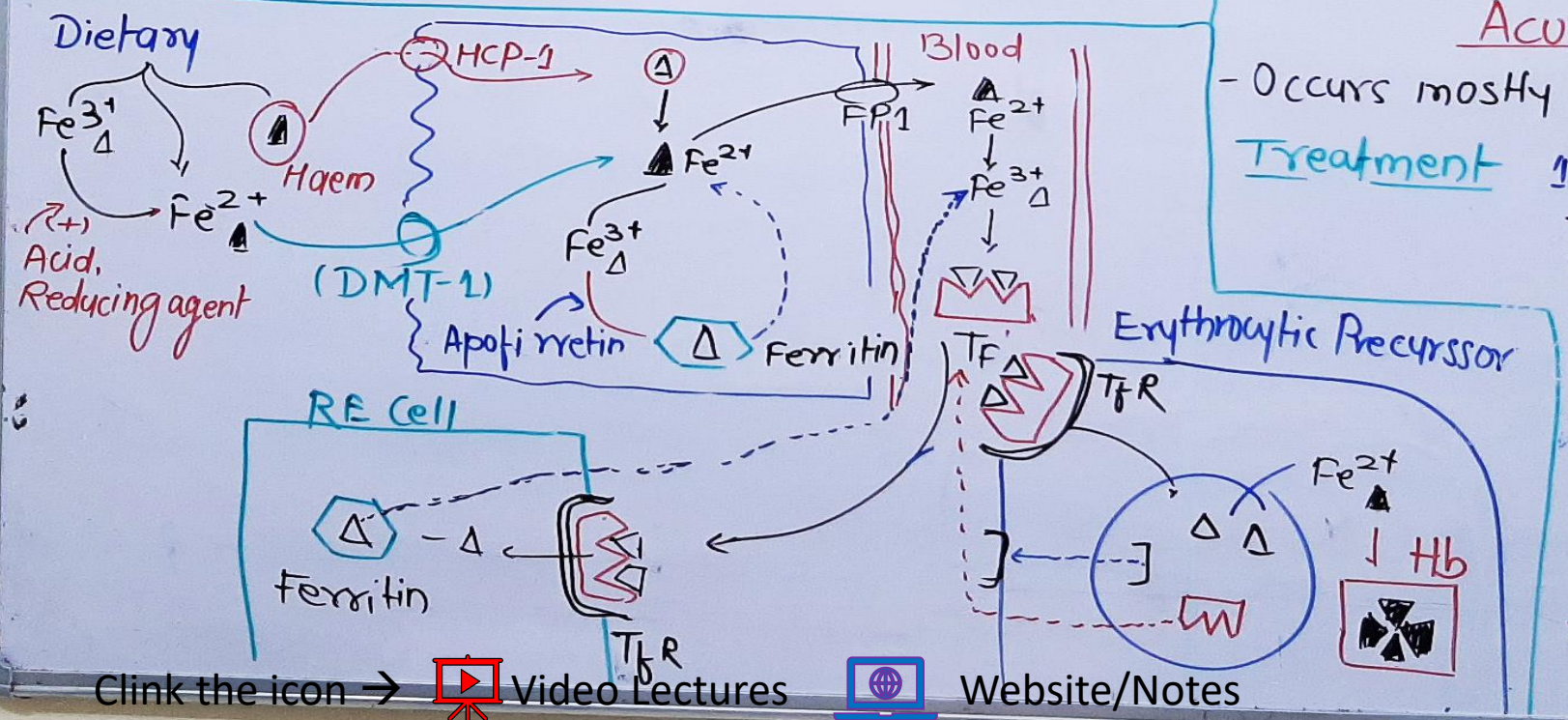
Haematinics :- Iron, Vit. B12, Folic Acid, Erythropoietin

"IRON"

↳ Total body iron - 2.5 - 5.0 g [M - 50mg/kg, F - 38 mg/kg]

↳ Hb (62.1.), Ferritin & Haemosiderin (25.1.), Myoglobin (7.1.), Enzymes (6.1.)

↳ Daily Need = M = 0.5 - 1 mg, F = 1 - 2 mg



ORAL PREPARATIONS

Ferrous Sulfate - hydrated Salt - 20.1., Dry - 32.1. Fe^{2+}
Ferrous Gluconate - 12.1. Fe^{2+}
Ferrous Fumarate - 33.1. Fe^{2+}
Colloidal Ferric hydroxide - 50.1 Iron

Fe^{2+} + Vit B complex + Folic a + Zink

ADR - Epigastric pain, Nausea, Heartburn, Bloating teeth staining, metalic taste, colic

PARENTERAL IRON - Iron dextron (Im)

ADR - Fever, Joint pain, Palpitation, Lymph node enlargement, dyspnoea

Uses :- Iron-Deficiency & Megaloblastic Anemia

ACUTE IRON POISONING

- Occurs mostly in infants & children :- >60mg/kg

Treatment

1. ↓ Absorption by-
   → Vomiting, Gastric lavage
   → Egg yolk, milk,
2. Chelating Agents
   - Desferrioxamine (1st choice)
     ↳ 0.5 - 1 g, im injection
   - DTPA
   - Ca. Edetate

* BAL = Contraindicated

HAEMATINICS : BLOOD FORMING AGENTS

Vit B12 & Folic Acid - Maturation Factors

Deficiency → Megaloblastic Anaemia (Macrocytic Anemia)

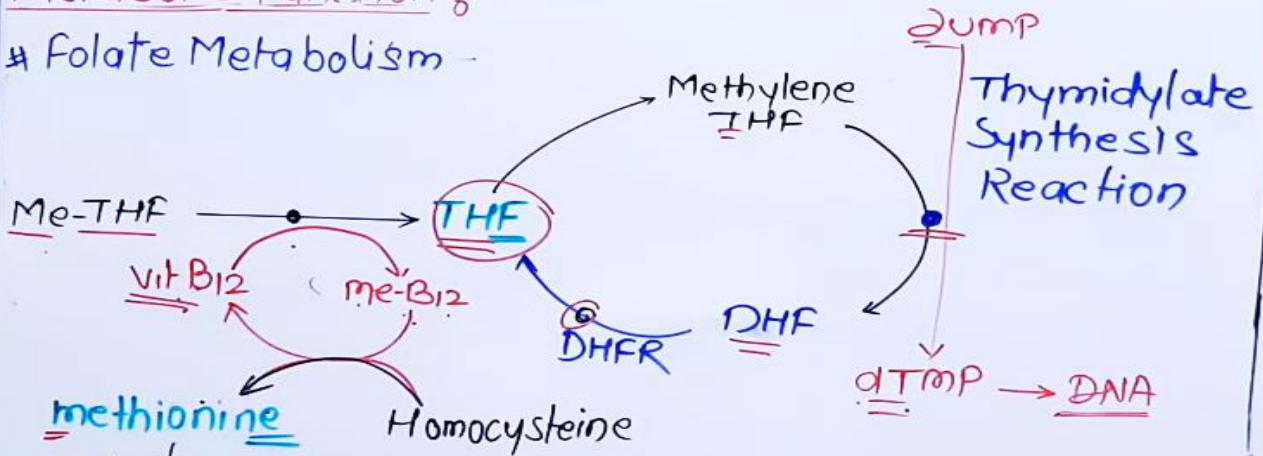
"Vit B12 : Cyanocobalamine/Hydroxocobalamine"

↳ Daily Req. → 1-3 ug, Pregnancy - 3-5 ug

↳ Source → Animals (Liver, meats, fish, etc), Plants (Pulses)

Metabolic function :-

Folate Metabolism -



Malonic ā —DAB12→ Succinic ā

↳ Accumulatn → Demyelination

Methionine —DAB12→ S-adenosyl methionine → synthesis

↓ neurological Damage (phospholipids & Myelin)

UTILIZATION - B12 + IF — Transcobalamine → Blood — BM & Liver

Excreted through bile (3-7 ug/day)

± Enterohepatic circulatn - 0.5-1 ug - Reabsorbed

Preparations - Cyanocobalamine (35 ug/1 ml inj)

Hydroxocobalamine (500 ug, 1000 ug, injection)

Prophylactic dose - 3-10 ug/day orally

Therapeutic dose - HC (1 mg inj) daily or alternate days for two weeks or till Neurological symptoms

Neurological :- degeneration of spinal cord, peripheral neurities, paresthesia, depressed stretch reflex, muscular weakness, poor memory, mood changes, hallucination.

↳ Methyl B12 - 0.5 - 1.5 mg/day to improve neurological function.

Uses :- ↳ Megaloblastic Anaemia

↳ Vit B12 Deficiency - Neurological dysfunction (Neuropathies, Psychiatric disorder, etc)

↳ Mega dose 5g for ↓ cyanide poisoning due to Sever Smoking

ADR :- Allergy or Anaphylactic Reaction

HAEMATINICS : BLOOD FORMING AGENTS

FOLIC ACID

↳ Yellow Crystal Insoluble in water while sod. salt Freely soluble in water.

↳ Chemically - Pteroyl Glutamic Acid (PGA)

↓

Pteridine + PABA + Glutamic acid

↳ 'Wills' had found that liver extract contained a factor other than VitB12, which could cure Megaloblastic anemia.

↳ "Mitchell" in 1941 isolated an antianemia principle from spinach and called Folic acid

↳ Daily Requirement = < 0.1 mg

↳ Dietary Source - Green leafy Veg., Egg, Meats

Utelization :→ Diet → Polyglutamate

(Body Store - 5-10mg)

↓ F. Conjugase

Mono & Diglutamate

m-THF (Bile Exc.) Enterohepatic Circulation Duodenum

Taken up by liver

MG & D.G

↓

T.H.F (MG)

↓

Methyl-THF

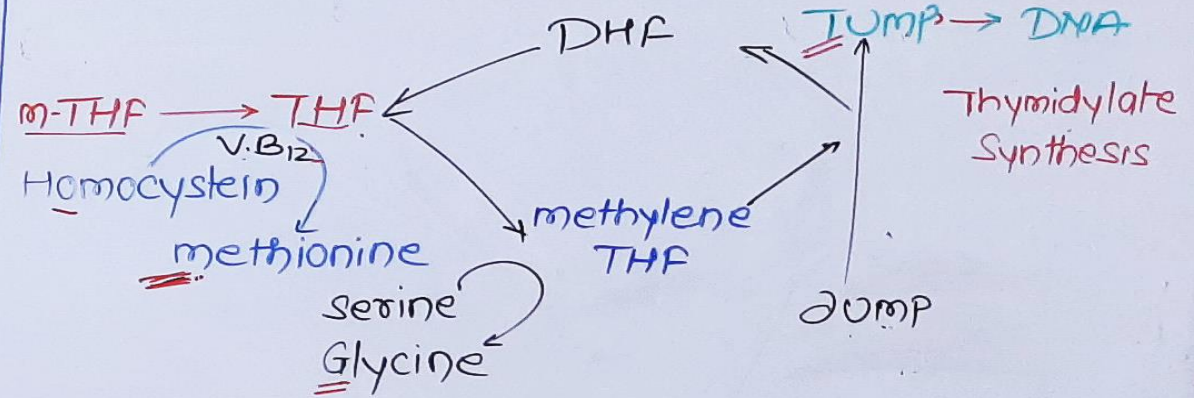
PA Transport System

↑

Polyglutamate ← m-THF

Metabolic function —

FA —FR→ DHFA —DHFR→ THFA # Essential for Thymidylate Syn.



Deficiency → 1) Megaloblastic Anemia

2) Epithelial damage - glossitis, Enteritis

3) Neural tube defect -

4) General debility, weight loss, sterility

Preparations - Orall, injectable with others

Uses: — 1) Megaloblastic anaemia — deficiency → malabsorption, ↑ demand, Antiepileptic therapy

2) Prophylaxis

3) Anticancer / MTX Therapy

4) Citrovorum factor rescue

ADR - injectable may cause local Sensetivity

ERYTROPOIETIN

- Erythropoietin (EPO) is a Sialoglycoprotein hormone (MW 34000) produced by peritubular cells of Kidney & that is essential for the Erythropoiesis.

↳ Anemia/Hypoxia ⊥ Kidney $\xrightarrow{(+)}$ EPO Secretion

↳ EPO acts as a Erythroid marrow & →

Ⓐ Stimulate proliferation of colony forming cells of the erythroid Series

Ⓑ Induce haemoglobin formation and erythroblast maturation.

MOA :-

EPO ⟶ EPO-R (JAK-STAT) ⟶ Transcription factors ↓ Gene Expression ↓ ↑ Erythropoiesis

Recombinant drug =

(Epoetin α, β) - IV, SC, $t_{1/2}$ = 6-10h

(Darbepoetin α) - hyperglycosylated modified preparat" of Epo $t_{1/2}$ = 24-36 h

USES :-

↳ Anemia of chronic Renal failure Hb ≤ 8 g/dL
(Epoetin 25-100 U/kg, SC/IV, 3times in a week)

↳ Anemia :-
- AIDS patients treated with Zidovudin
→ Cancer Chemotherapy induced Anemia
→ Surgery induced Anemia

ADR :- Epo is a non-immunogenic. ADR are related to Sudden increase in Haematocrit, blood Viscosity, Peripheral vascular Resistance

↳ Clot formation
↳ Hypertension
↳ Thromboembolic events
↳ Seizure
↳ Flu-like Symptoms

COAGULANTS / HAEMOSTATIC AGENTS

"Haemostasis (arrest of blood loss) & Coagulation involve complex interaction b/w the injured blood vessel wall, Platelet, & Coagulation Factors

Coagulation Pathways –

① Intrinsic → Contact activation of Hagemen Factor
② Extrinsic → Tissue Thromboplastin (Need TF)

Coagulatn Factors - present in plasma in the inactivated form (Zymogen). By proteolysis they themselves become an active protease and activate the next factor

HAEMOSTATIC AGENTS – improve haemostasis by stimulating Fibrin formation and/or reducing Fibrinolysis. Like C.F. & Coagulants

Factors – Antithrombin, Protein-C, Protein-S, Antithromboplastin & Fibrinolysin system tend to oppose Coagulation and lyse Formed clott

Coagulation ⇌ Anti Coagulation

Coagulants –

① Whole Blood Plasma → Indicated in C.F. Deficiency

② Vit. K = act as a co-factor at late stage in synthesis by liver of Coag Factors.

II – Prothrombin
VII – Proconvertin
IX – Christmax Factor
X – Stuart Factor

K_1: Plants = Phytonadione (Phylloquinone)

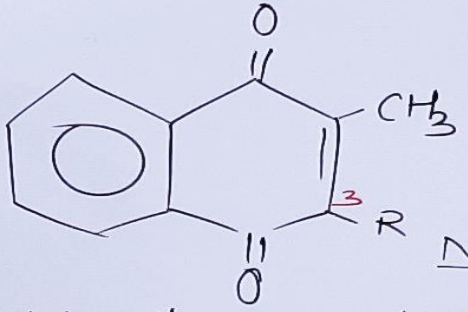
K_3 - Synthetic

Fat-Soluble - Menadione, Acetomenaphthone
Water Soluble – Menadione Sod. bisulfite

③ Others: – Fibrinogen, Rutin, Desmopressin, Antihaemophilic factor, Adrenochrome monosemicarbazone, Etham sylate

Clink the icon → Video Lectures Website/Notes

VITAMIN-K



R = Phytyl = K_1
R = Prenyl = K_2
R = -H = K_3

Naphthoquinone Struc.

Fat Soluble vit., essential for Synthesis of clotting Factors (II, VII, IX, X)

Dam (1929) - produced bleeding disorder in chicken by Feeding deficient diet.

This was due to ↓ level of Prothrombin that was cured by Fat soluble fraction of hog liver

Alfalfa Grass → K_1 (Phytonadione), 1939

Sardine (Sea Fish) → K_2

K_2 (Menaquinone) - produced by colony bacteria.

Synthetic Form - K_3 (Menadione)

Daily Req.:- 50-100 µg/day

Action:- vit K acts as a cofactor at a late stage in the synthesis by Liver of coagulation proteins -

↳ Prothrombin (II) ↳ Christmas Factor (IX)

↳ Proconvertin (VII) ↳ Stuart-Factor (X

2 7 9 10

UTELIZATION - fat soluble vit K, absorbed from intestine via lymph and require bile salt for absorption. while water soluble vit absorbed directly into portal blood.

K_1 = Active Transport System

K_2/K_3 = Simple diffusion

vit K conc. in liver but no significantly store in body, metabolized by liver by side chain cleavage & glucuronide & Exc. by bile & Urine

Deficiency by - Liver disease, Jaundice, Malabsorption, chronic Antibiotic Therapy.

Uses:- Prophylaxis/Treatment of bleeding disorder due to deficiency of clotting factors in Following situation -

↳ ↓ dietary intake, ↳ chronic AMA Therapy

↳ Liver disorders, ↳ New born

↳ Overdose of Anticoagulants & Aspirin therapy

ADR - K_1 = Allergy, Sever Anaphylactoid reaction

K_2 = Hemolysis in G6PD deficient patient

ANTI-COAGULANTS

These drugs are used to reduce the coagulability of Blood.

I. PARENTERAL ANTICOAGULANTS

A. Indirect Thrombin Inhibitors
- Heparin (unfractionated)
- Low Mol. Weight Haperins - Enoxaparin, Reviparin, Nadroparin, Dalteparin, Parnaparin, Ardeparin.
- Fondaparinux
- Danaparoid

B. Direct Thrombin Inhibitors
- Bivalirudin, Argatroban

II. ORAL ANTICOAGULANTS

A. VIT K Antagonists
- Warfarin Sodium.,
- Bishydroxy coumarin (dicumarol)
- Acenocoumarol
- Ethyl-Bis coumacetate

B. Direct Factor X_A Inhibitor
- Rivaroxaban, Apixaban

C. Oral Direct Thrombin Inhibitor
- Dabigatranetexilate

	Heparin	Warfarin
chem. →	Sulfated Polysac. of D-glucosamine-D-glucuronic acid	Coumarine der.
MOA -	↑ Activity of Antithrombin III → (−) Factor IIa & Xa	↓ synthesis of Vit K-dep. C.F. - II, VII, IX, X
Kinetic →	IV/sc, hepatic & reticuloendothelial eliminatn, t_2 = 2h	orally, 98% PB, Liver metabolism, $t_{\frac{1}{2}}$ = 36h
Antagonist -	Protamine Sulfate	vitamin K
Uses →	Thrombosis, Embli unstable Angina	Thrombosis, embli, Post-MI. Heart Valva damage.
ADR ⇒	Bleeding, Hypersensetivity Osteoporosis	Alopacia, dermetitis, Teratogenic.

Clink the icon → Video Lectures Website/Notes

HEPARIN PHARMACOLOGY

Parenteral Anti-Coagulant

Mclean – discovered in 1916 – Liver contains powerful anticoagulant. Howell & Holt (1913) named "Heparin", Clinically used in 1937

Chemistry :– Mucopolysaccherides with M.W. 10000 to 20000. It contains of polymers of two sulfated disaccharide unit.

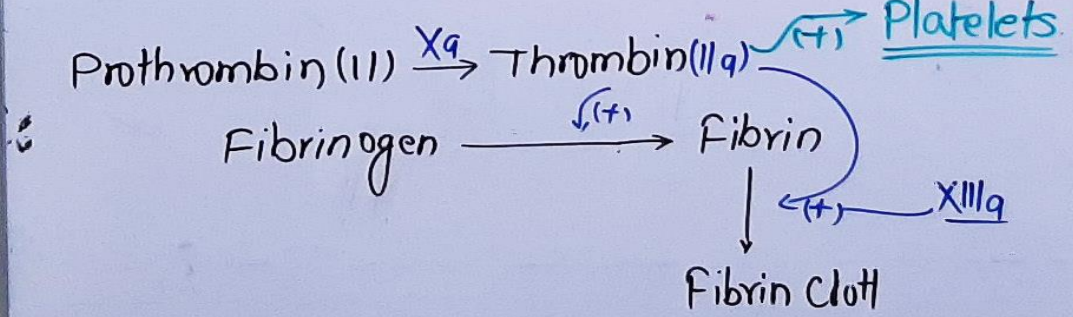
- D-Glucosamine – L- iduronic acid
- D-Glucosamine – D- Glucuronic acid

present in mast cell, richest source are lungs, liver, & intestinal mucosa.

PHARMACOLOGY ⇒ "Effective in-vivo & in-vitro"

Heparin ⟶ Indirectly (+) Antithrombin III (a serin protease inhibitor) – Heparin – AT III (⟶)

(2, 9 10 11 12 13) Xa IIa IXa XIa XIIa XIIIa



Heparin enhances AT III by two way

1) provides scaffolding for the CF Xa & IIa on one hand & AT III on other
2. induces confirmational changes in AT III to expose it interactive site (pentasacc. Hep. – has high affinity to AT III to induce conformational changes, this has been synthesised & named "Fondaparinux"

Antiplatelet action & # Lipaemia Clearing

P'KINETIC – iv/sc, Not cross BBB & Placenta, metabolised by heparinase (Liver) & Exc. through urin, t1/2 (1-4h)

ADR – Bleeding, Thrombocytopenia, Alopecia, Osteophoresis

Contraindicatn – Bleeding disorder, Sever hypertension Subacute bac. endocarditis, Ocular/Neurosurgery

Uses – MI/Angina
Thrombosis
As Antiplatelet
Lepaemia clearing
Rheumatic Heart disease
Cerebrovascular disease
Defibrination Syndrome

LOW MOLECULAR WEIGHT HEPARIN

↳ Heparin has been Fractionated into LMW form (5000 – 7000 MW)

↳ They have different anticoagulant profile ie. selectively inhibit CF X_a with little effect on CF IIa.

↳ They act only be inducing conformational changes in AT III. Thus they have lesser anticoagulant & antiplatelets effects.

Pkinetic → Better S.C. Bioavailability (~70 – 90%) as compared to UFH (20 – 30%)

↳ longer $t_{1/2}$ = 4–6 h & aPTT/clotting time are not prolonged.

ADR – Lesser adverse effect incidence like – Bleeding, haemorrhage, Thrombocytopenia, Osteoporosis

Uses – They show similar efficacious as UFH. except during cardiopulmonary pass Surgery due to lesser effective in preventing catheter thrombosis

→ Prophylaxis of deep vein Thrombosis (DVT)
→ Established DVT treatment
→ Unstable angina & MI

LMW Heparin – Enoxaparin, Reviparin, Nadroparin Dalteparin, Parnaparin.

FONDAPARINUX

Pentasaccharide derivative having highly affinity to induce irreversible conformational changes in AT III to inactivates CF X_a

S.C. BA = 100%, $t_{1/2}$ = 17h, minimal metabolism Excreted throug urine.

It can not be used in Renal Failure patient

It has lesser incidence of ADR

Uses = Prophylaxis & treatment of DVT
= Acute coronary Syndrome

Protamine Sulfate

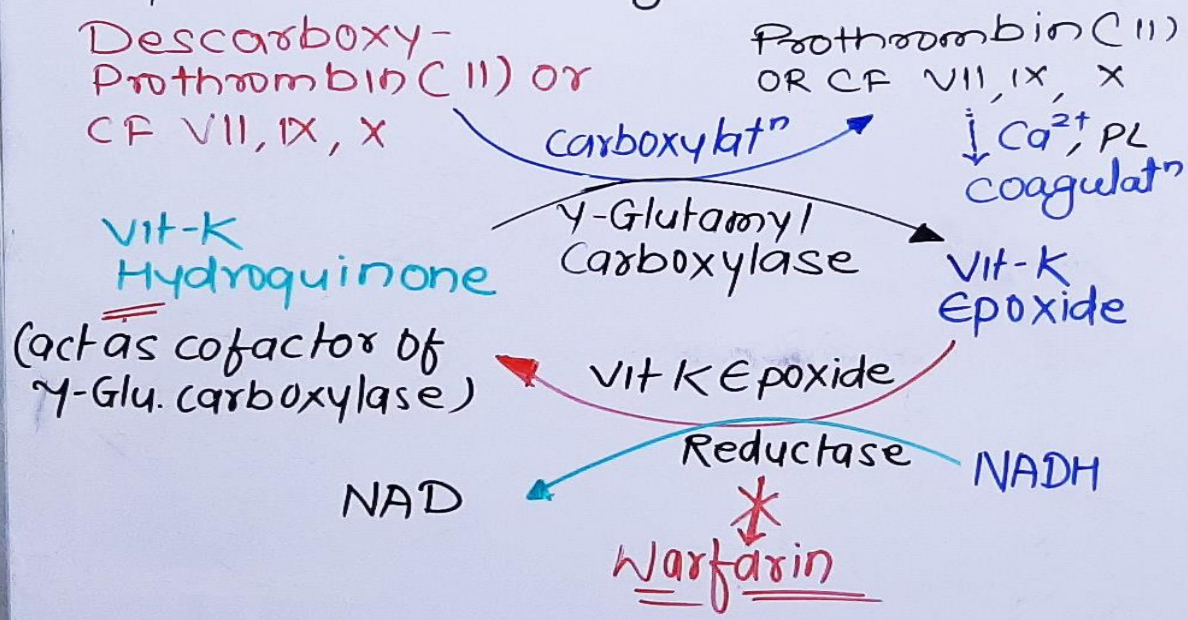
– Strong base, LMW protein obtaine from sperm of Fishes

→ Neutralised the effect of heparins 1mg IV = 100 U Hep.

WARFARIN PHARMACOLOGY

ORAL ANTICOAGULANTS, # IN-VIVO ONLY

MOA :→ Indirect Inhibit the synthesis of Vit-K dependent clotting factors (II, VII, IX, & X)
↓ protein C & S, Osteocalcin
Competitive Vit K Antagonist



Warfarin inj → ↓ level of clotting factor
VII ($t_{\frac{1}{2}}$: 6h) ···· IX (24h) -- X (40h) --- II (60h)

For therapeutic effect, CF synthesis should be inhibited upto 40-50%.
RS-Warfarin (Racemic mix) - Comercial preparation
Activity = S-Warfarin > R-warfarin

ADR :- Alopecia, Dermatitis, diarrhoea, GI bleeding Heaturia, internal hemorrhage

Uses - Thrombosis, pulmonary Embolism, MI, DVT, Prosthetic Heart Valves disease.

Factor ↑Effects – Malnutrition, AMA Therapy, Liver disease (↓CF), Hyperthyroidism (↑ degradatn of CF)

Factor ↓ effect – Pregnancy (↑CF), Nephrotic synd. Genetic warfarin resistance

DRUG INTERACTION :-

A. **Enhanced Action** – Broad Spectrum Antibiotic, Aspirin, PB displacement (Sulfonamide, phenytoin, indomethacin, probanacid), Enz inhibitor (chloremphenicol, cimetidine, erythromycin, allopurinol, amiodarone, etc)
"COKE P INH"

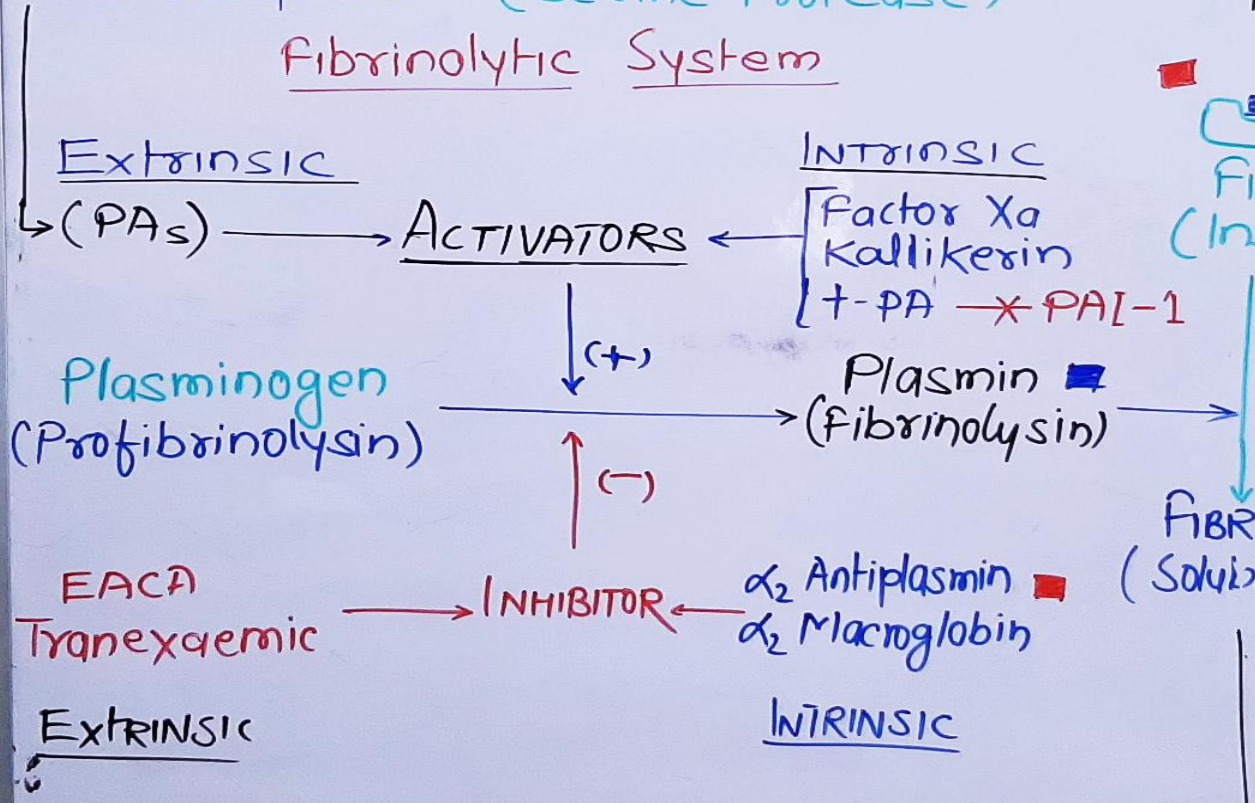
B. **Decreased Action →** Metabolic Enz inducer- (Barbiturate, Gresiofulvin, Rifampin) oral contraceptives
"GPRS Cell Phone"

FIBRINOLYTICS OR THROMBOLYTICS DRUGS

The drugs, which lyse thrombi/clot to recanalize occluded blood vessels (coronary artery).

↳ Streptokinase (STK) – β-hemolytic streptococci
↳ Urokinase (uPA) – Serine protease (kidney & Urine)
↳ Recombinant (tPA) – Alteplase, Reteplase, & Tenecteplase – (Serine Protease)

Fibrinolytic System



FIBRIN (Insoluble)

FIBRIN (Soluble)

\# Venous thrombi are more easily lysed by Fibrinolytic than artery

Uses – Thrombosis, Deep Vein thrombosis, Acute M.I., Pulmonary Embolism, Stroke, Peripheral Arterial occlusion

ADR – Antigenic action, Allergy, Bleeding, Hypotension & Arrhythmia

contraindications –

\# Subacute Bacterial Endocarditis
\# Hemophelia / Bleeding disorder
\# Cerebrovascular Disease
\# Brain tumors
\# Aneurysm
\# Uncontrolled hypertension

ANTI-PLATELET DRUGS

Aspirin :- Irriversible inhibit the COX-I in platelet & ↓ TXA_2-mediated Platelet Aggregation. → "↓ TXA_2 & Platelet Activat^n"

↳ ↑ bleeding or ↑ blood Cloting time

USES: → At low Dose (150-375mg) → Angina, MI, Atherosclerosis & ↓ incidence of Colon Cancer. At high dose (1g) → Antiinflammatory, Analgesic, Antipyratic ["NSAID"]

ADR - GI bleeding, Raye's Syndrome & Tinitis

CLOPIDOGRES :- Block the ADP-mediated Platelet Aggregation by Antagonising P_2Y_{12}-Receptor and further ↓ GpIIb/IIIa expression

USES: → Thrombotic stroke, Unstable Angina, MI, Acute Coronary Syndrome, Atherosclerosis

ADR(Ticlopidine) → Neutropenia, Thrombocytopenia

ABCIXIMAB :- Antagonise the GpIIb/IIIa Receptor on activated Platelet & prevent platelet aggregation.

USE - Acute Coronary Syndrome

ADR - Bleeding, Thrombocytopenia

PDE-III Inhibitors - Dipyridamol, Cilostazol

↳ ↓ Phosphodiesterase III → ↑ cAMP → ↓ Platelet Aggregation

USE - Angina, Prevent Stroke

ADR - GI upsale, Palpitation, Facial Flussing, Hypotension

PLASMA VOLUME EXPANDERS

Agents that expand the plasma volume by increasing the osmotic pressure.

Agents – Human Albumine, Dextran, Degraded gelatin polymer, Hydroxyethylcellulose(HEC), Polyvinylpyrrolidone (PVP)

MOA = These are highly molecular weight subs. which exert colloidal osmotic pressure, & when infused IV retain fluid in the vascular Compartments.

Desirable property :→

should exert osmotic pressure comparable to plasma
Should remain in the circulation
Should P'dynamically inert
should not be pyrogenic & antigenic
should not be interfere with blood grouping
should not contain any infective agents
should be stable and easily sterilizable

Human Albumine

20% of H.albumin (100ml) solution is osmotic equivelent of about 400ml of fresh frozen plasma or 800ml of whole blood.

DEXTRAN

It is polysaccharide obtained from Sugar beat, which is available in two form –

1 Dextran-70 – (MW 70000) HMW
2 Dextran-40 – (MW 40000) LMW

Dextran-70 most commonly used, it expand plasma vol. for nearly 24h, it slowly exc. by Glomerular Filteration. It contains all properties except :-
↳ It may interfere with blood grouping &
↳ Sometimes interact with antibodies and elict allergic response
↳ Interefere with coagulation & platelet functn

Dextran-40 - It act more rapidly, it reduces blood viscosity & prevent RBC Sludging, improve microcirculation. However, rapidly excreted & has shorter duration of action

Uses – Burn, Hypovolumic & endotoxin shock, sever trauma, & extremly tissue Damage

Contraindication – Sever Anemia, Cardiac Failure, Pulmonary Edema, Renal Failure