Coagulant, Anticoagulant, Fibrinolytic, Antifibrinolytic and Antiplatelet

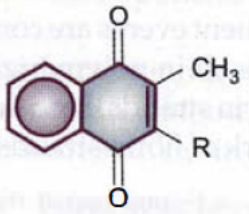
Coagulants

- These are substances which promote coagulation, and are indicated in haemorrhagic states.
- Fresh whole blood or plasma provide all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor; also they act immediately.
- Other drugs used to restore haemostasis are:

1. Vitamin K and
2. Miscellaneius

1. ***Vitamin K***

K_1 (from plants, fat-soluble)	:	Phytonadione (Phylloquinone)
K_3 (synthetic)		
—Fat-soluble	:	Menadione, Acetomenaphthone
—Water-soluble	:	Menadione sod. bisulfite
	:	Menadione sod. diphosphate



VITAMIN K

2. ***Miscellaneous***

Fibrinogen (human)
Antihaemophilic factor
Desmopressin
Adrenochrome monosemicarbazone
Rutin, Ethamsylate

Vitamin K

- It is a fat-soluble dietary principle required for the synthesis of clotting factors.

Action

- Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins prothrombin, factors VII, IX and X.
- The vit K dependent change **(γ** carboxylation of glutamate residues of these zymogen proteins**)** confers on them the capacity to bind Ca2+ and to get bound to phospholipid surfaces-properties essential for participation in the coagulation cascade.

Vitamin K

Toxicity

Rapid i.v. injection of emulsified vit K produces flushing, breathlessness, a sense of constriction in the chest, fall in BP; few deaths are on record. It is probably due to emulsion form of the preparation.

Anticoagulants

- These are drugs used to reduce the coagulability of blood.
- They may be classified into:

1. Used in vivo and
2. Used in vitro

I. Used in vivo

A. *Parenteral anticoagulants*
Heparin, Low molecular weight heparin.
Heparinoids—Heparan sulfate, Danaparoid, Lepirudin, Ancrod.

B. *Oral anticoagulants*

(i) *Coumarin derivatives*: Bishydroxycoumarin (dicumarol), Warfarin sod, Acenocoumarol (Nicoumalone), Ethylbiscoumacetate

(ii) *Indandione derivative*: Phenindione.

II. Used in vitro

A. Heparin:
150 U to prevent clotting of 100 ml blood.

B. Calcium complexing agents:
Sodium citrate: 1.65 g for 350 ml of blood; used to keep blood in the fluid state for transfusion; **ANTICOAGULANT ACID CITRATE DEXTROSE SOLUTION 2.2 g/100 ml** (75 ml is used for 1 unit of blood).
Sodium oxalate: 10 mg for 1 ml blood
Sodium edetate: 2 mg for 1 ml blood
} used in blood taken for investigations

Heparin

- Is a powerful and instantaneously acting anticoagulant.
- It acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor).
- The heparin-AT III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them.
- The anticoagulant action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.

Heparin

- Low concentrations of heparin prolong aPTT without significantly prolonging PT. High concentrations prolong both.
- Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.
- Heparin is anticoagulant of choice during pregnancy (does not cross BBB and placenta) while warfarin is contraindicated during pregnancy.

Heparin: Adverse effect

1. Bleeding due to overdose is the most serious complication of heparin therapy. Haematuria is generally the first sign.
2. Thrombocytopenia is another common problem.
3. Transient and reversible alopecia is infrequent. Serum transaminase levels may rise.
4. Osteoporosis may develop on long-term use of relatively high doses.
5. Hypersensitivity reactions are rare-urticaria, rigor, fever and anaphylaxis. Patients with allergic diathesis are more liable.

Low Molecular Weight Heparin

- Heparin has been fractionated into LMW forms (MW 3000-7000) by different techniques.
- LMW heparins have a different anticoagulant profile; selectively inhibit factor Xa with little effect on IIa.
- Indications of LMW heparins are:

1. Prophylaxis of deep vein thrombosis and pulmonary embolism in high-risk patients undergoing surgery; stroke or other immobilized patients.
2. Treatment of established deep vein thrombosis.
3. Unstable angina.

Property	Unfractionated Heparin	LMW heparin
Molecular weight range	3000-30000	1000-9000
MOA	Inactivates factor Xa and IIa	Inactivates factor Xa
Lab monitoring	aPTT	Not required
Dosage	Adjusted as per aPTT	Fixed; 40 mg and 60 mg
Routes	IV, SC	SC only

Heparin Antagonist

- **Protamine sulfate** It is a strongly basic, low molecular weight protein obtained from the sperm of certain fish.
- Given i.v. it neutralises heparin weight for weight, i.e. 1 mg is needed for every 100 U of heparin.
- Protamine is more commonly used when heparin action needs to be terminated rapidly, e.g. after cardiac or vascular surgery.

Warfarin: oral anticoagulants

- Warfarin and its congeners act as anticoagulants
- they act indirectly by interfering with the synthesis of vit K dependent clotting factors in liver.
- interfere with regeneration of the active hydroquinone form of vit K which carries out the final step of y carboxylating glutamate residues of prothrombin and factors VII, IX and X.
- This carboxylation is essential for the ability of the clotting factors to bind Ca2+ and to get bound to phospholipid surfaces, necessary for coagulation sequence to proceed.
- Dose regulation: PT -INR

Adverse Effect

- Bleeding as a result of extension of the desired pharmacological action is the most important problem: ecchymosis, epistaxis, hematuria, bleeding in the g.i.t. Intracranial or other internal haemorrhages may be fatal.

Treatment: of bleeding due to oral anticoagulants consists of:

- Withhold the anticoagulant.
- Give fresh blood transfusion: supplies clotting factors and replenishes-lost blood. Alternatively fresh frozen plasma may be used as a source of clotting factors.
- Give vit K1-specific antidote, but it takes 6-24 hours for the clotting factors to be resynthesized and released in blood after vit K administration.

Uses of anticoagulants

1. Deep vein thrombosis and pulmonary embolism
2. Myocardial infarction (MI)
3. Unstable angina
4. Rheumatic heart disease; atrial fibrillation
5. Cerebrovascular disease
6. Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis
7. Defibrination syndrome or disseminated intravascular caogulation

Table 44.2: Some comparative aspects of heparin and oral anticoagulants

	Heparin	*Warfarin*
1. Chemistry	Mucopolysaccharide	Coumarin derivative
2. Source	Hog lung, pig intestine	Synthetic
3. Route of admin.	Parenteral (i.v., s.c.)	Oral
4. Onset of action	Immediate	Delayed (1–3 days)
5. Duration of action	4–6 hrs	3–6 days
6. Activity	*In vitro* and *in vivo*	*In vivo* only
7. Mechanism	Blocks action of factor X and thrombin	Inhibits synthesis of clotting factors
8. Antagonist	Protamine sulphate	Vit K
9. Variability in response	Little	Marked
10. Lab. control	a PTT/clotting time (desirable)	Prothrombin time/INR (essential)
11. Drug interactions	Few and not significant	Many and significant
12. Use	To initiate therapy	For maintenance

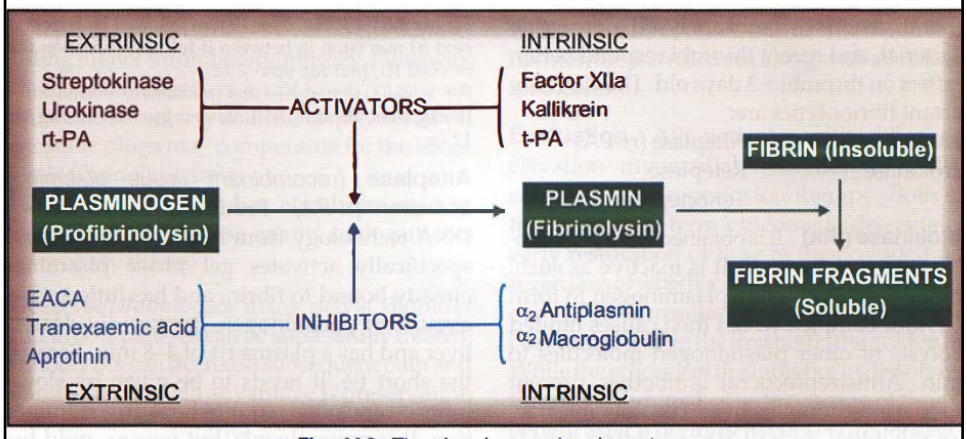


Fig. 44.3: The plasminogen-plasmin system

Fibrinolytics (Thrombolytics)

- These are drugs used to lyse thrombi / clot to recanalize occluded blood vessels (mainly coronary artery).
- They are curative rather than prophylactic; work by activating the natural fibrinolytic system
- The clinically important fibrinolytics are:
  1. Streptokinase
  2. Urokinase
  3. Alteplase
  4. Reteplase
  5. Tenecteplase

Streptokinase
For MI: 7.5-15 lac IV infused i.v. over 1 hr.
For deep vein thrombosis and pulmonary embolism: 2.5 lac IU loading dose over '12-1 hr, followed by 1 lac IV/hr for 24 hr.

Urokinase
For MI: 2.5 lac IU Lv. over 10 min followed by 5 lac IU over next 60 min (stop in between if full recanalization occurs) or 6000 IV/min for upto 2 hr.
For venous thrombosis and pulmonary embolism: 4400 IV/kg over 10 min Lv. followed by 4400 IV/kg/hr for 12 hr.

Alteplase (rt-PA: recombinant tissue plasminogen activator)
For MI: 15 mg Lv. bolus injection followed by 50 mg over 30 min, then 35 mg over the next 1 hr.
For pulmonary embolism: 100 mg i.v. infused over 2 hr.

Uses of fibrinolytics

- Acute myocardial infarcation
- Deep vein thrombosis
- Pulmonary embolism
- Peripheral arterial occlusion
- Stroke

Antifibrinolytics

- These are drugs which inhibit plasminogen activation and dissolution of clot.

Drugs:

- Epsilon amino caproic acid (EACA)
- Tranexaemic acid

MOA

- Binds to lysine binding site on plasminogen & plasmin and thus prevents its binding to fibrin and lysed it.

Uses and Adverse effect of Tranexaemic acid

Uses

- Overdose of fibrinolytics
- After cardio-pulmonary bypass surgery.
- After tonsillectomy, prostatic surgery, tooth extraction in haemophiliacs.
- Menorrhagia, specially due to ruCD.
- Recurrent epistaxis, ocular trauma, bleeding peptic ulcer.

Main side effects are nausea and diarrhoea. Headache, giddiness and thrombophlebitis of injected vein are other adverse effects

Antiplatelets

- These are drugs which interfere with platelet function and are useful in the prophylaxis of thromboembolic disorders.
- The clinically important antiplatelet drugs are:

1. Aspirin
2. Dipyridamole
3. Ticlopidine
4. Clopidogrel
5. Abciximab (GP IIb /IIIa antagonist)

Aspirin

- inhibits the enzyme COX and TX-synthase-inactivating them irreversibly.
- TXA2 formation is suppressed at very low doses and till fresh platelets are formed. Thus, aspirin induced prolongation of bleeding time lasts for 5-7 days.
- Aspirin inhibits the release of ADP from platelets and their sticking to each other.

Dipyridamole

- Dipyridamole It is a vasodilator which was introduced for angina pectoris**.**
- It inhibits phosphodiesterase and blocks uptake of adenosine to increase platelet cAMP which potentiates PGI2 and interferes with aggregation.
- Dose: 150-300 mg/ day.

Ticlopidine

- alters surface receptors on platelets and inhibits ADP as well as fibrinogen-induced platelet aggregation.
- It prevents fibrinogen binding to platelets.
- Side effects: Diarrhoea, vomiting, abdominal pain, headache, tinnitus, skin rash.
- Serious adverse effects are bleeding, neutropenia, thrombocytopenia and jaundice. Several fatalities have occurred.

Dose: 250 mg BD with meals

Clopidogrel

- Similar mechanism of action as ticlopidine

Abciximab

- Glycoprotein (GP) IIb/IIIa receptor antagonists
- GPIIb/IIIa is a binding receptor for fibrinogen and vWF.
- The main risk is haemorrhage;Thrombocytopenia is another complication. Constipation, ileus and arrhythmias can occur.

Uses of Antiplatelet

- Coronary artery disease
- Cerebrovascular disease
- Coronary angioplasty, stents, bypass implants
- Prosthetic heart valves and arteriovenous shunts
- Venous thromboembolism
- Peripheral vascular disease