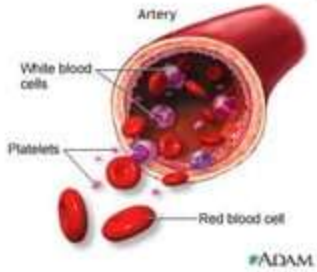
NEIGRIHMS



Drugs Affecting Coagulation and Anticoagulants

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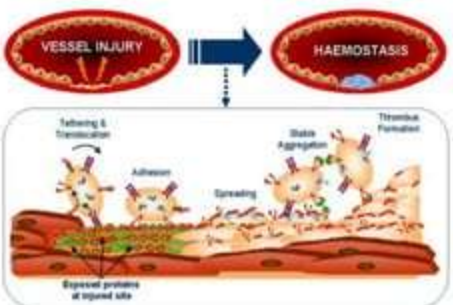
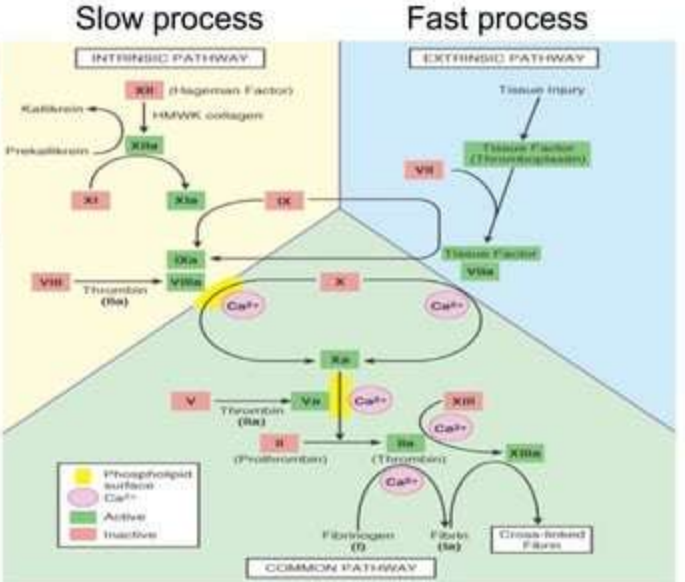
Haemostasis

- BLEEDING !!! .....
- **Haemostasis: Arrest of Bleeding -** The Physiological mechanism which results in stoppage of bleeding after an injury
- **Primary haemostasis:** platelet aggregation - platelet plug formation (plus local vasospasm) – sealing of gap
- **Blood clotting:**
  - Intrinsic: within blood vessels
  - Extrinsic pathway: extravagated blood
- **Secondary haemostasis: Stabilizes**
  - Intrinsic: prevents further escape of Blood
  - Extrinsic: plugs the gap in the blood vessels
- **Weak blood clot:** Without platelet aggregation

Coagulation cascade

Tests	PT	aPTT
Intrinsic	N (12 -14 s)	P
Extrinsic	P	N (26-32 s)
Common	P	P

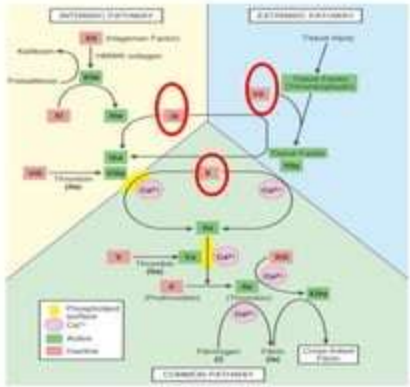




Thrombus Vs Embolus

- **Blood clots** – a clot adheres to blood vessels (usually arteriole) – **Thrombus**
- **Pathological !!!**
- Thrombus dislodges and floats in blood vessels from arteries and veins – **Embolus (Pathological)**
- **Emboli** can block arterioles in the lung and pulmonary circulation
  - **Thromboembolism:** May lead to Deep vein thrombosis (DVT), Myocardial infarction, Unstable angina, rheumatic heart disease and CVA
  - **Arterial Thrombosis :** Adherence of platelets to arterial wall - **White** in color - Often associated with MI, stroke and ischemia (fibrin clot)
  - **Venous Thrombosis:** In areas of stagnated blood flow (deep vein thrombosis), **Red** in color- Associated with Congestive Heart Failure, Cancer, Surgery

Coagulants



- Fresh whole Blood or plasma
- **Drugs:**
  1. Vitamin K (Vit. K)
     - From plants (fat soluble) K_1: Phytonadione (Phylloquinone)
     - Synthetic K_3: Fat soluble - Menadione, Acetomenaphthone

       Water soluble: Menadione sod. Bisulfite, Menadione sod. Diphosphate
  1. Miscellaneous: Human fibrinogen, Antihaemophillic factor, Desmopressin, Adrenochrome, Rutin, ethamsylate etc.

K_1 – plants (alfalfa) - *phytyl*, K_2 – sea fish (sardine) - *prenyl* and K_3 - synthetic

Vitamin K

- Daily Requirement ?
- Colonic Bacteria (menaquinone K_2): 50-100 mcg/day
- **MOA:**
  - Cofactor in liver for factor II, VII, IX and X
  - Vit.K dependent change (ɣ-corboxylation of glutamate – confers capacity to bind to Ca++)
- **Kinetics:**
  - Fat soluble – from intestine via lymph – needs bile salt
  - Water soluble – directly to portal blood
  - K1: by active transport
  - K2 and K3 – by passive diffusion
  - Metabolized in liver by chain cleavage and glucoronide conjugation

Vitamin K - contd.

- **Deficiency:** normally does not produce deficiency
  - Deficiency causes lack of prothrombin and others
  - Bleeding – 1st sign – haematuria, git, epistaxis
    - In New Born – Routinely given
    - Comatose patients: Patrenteral
    - Heavy antibiotic
    - Liver diseases
    - Obstructive jaundice
    - Malabsorption
- **Uses:** Malabsorption, Dietary deficiency, Obstructive Jaundice, Newborn baby and Overdose of oral anticoagulants (10 mg IM – 5 mg 4 hrly)
- **ADRs:** Flushing, breathlessness, fall in BP and sense of constriction in chest. Menadione K_3 – haemolysis – G6PD deficiency

Other Drugs

- Fibrinogen: Human - in haemophillia and Antihaemophillic factor globulin (AHG) deficiency
- AHG : human
- Desmopressin: factor VIII release – haemophillia
- Adenochrome monosemicarbazone: epistaxis, haematuria, retinal haemorrhage
- Ethamsylate: antihyaluronidase effect – haematuria, epistaxis, malaena, abortion , PPH and menorrhagia etc. – no action on fibrin formation

ANTICOAGULANTS

Anticoagulants - Classification

- Drugs used to reduce coagulability of Blood – Heparin and Vitamin K antagonists:
  - Used in vivo:
    - **Parenteral: Indirect thrombin inhibitor -** Heparin, Low molecular weight heparin (LMWH) and Heparinoids – Heparan sulfate, Danaparoid
      - **Direct TI** – Lepirudin, Bivalirudin and argatroban
    - **Oral anticoagulants:**
      - **Coumarin derivatives:** Bishydroxycoumarin (dicumarol), Warfarin sodium, Acenocoumarol and Ethylbiscoumacetate
      - **Indadione derivative:** Pheninidione
  - Used in vitro:
    - Heparin: 150 U for 100 ml of blood
    - Sodium citrate: 1.65 gm for 350 ml of blood: anticogulant acid citrate dextrose solution 2.2g/100 ml – 75 ml for 1 unit of blood

Heparin

- McLean
- Mixture of straight chain mucopolysaccharides with MW 10,000 to 20,000
- Contains polymers of two sulfated disaccharides: D-glucosamine-L-iduronic acid and D-glucosamine-D-glucoronic acid
- Strongest organic acid in our body – strong electronegative charge
- Mast cells – all tissues (75,000)
- Commercially – slaughter house - ox lung and intestine of Pig

Heparin - Action

- Powerful and instant action – in vitro in vivo
- Activates antithrombin III (inactivates thrombin) and similar cofactors
- Heparin-AT III complex – binds to Intrinsic and Common pathway – not VIIA (extrinsic)
- **Low conc.:** Xa mediated conversion of Prothrombin to thrombin affected
  - MOA: can be summarized as Inhibition of Xa and thrombin (IIa)
    - Prolongation of aPTT but no PT prolongation
    - High conc. – both prolonged
- AT III: Normally binds to protease factors – forms a stable factor (Suicide inhibitor)- procoagulant – slow
    - Long heparin molecules provide: 1) scaffolding for Xa and IIa also AT III
      2) Induces conformational change at AT III
    - Inhibition of Xa Vs Inhibition of IIa – selective Xa inhibition by LMWH
- Lipaemic action and antiplatelet action

Heparin – contd.

- **Kinetics:** Highly ionized and large – not absorbed. Given IV or SC – takes 60 min on SC
  - Does not cross BBB or placenta (pregnancy-thrombophlebitis !)
  - Mast cell release – destroyed by macrophages
  - Half life – 1 hr after IV – long among cirrhotic and kidney diseases
- **Unitage:** Variable molecular size – bioassay
  - 1 U = prevents 1ml of citrated sheep plasma for 1 hr (0.2 ml of $CaCl_2$ 1%)
  - Heparin sodium: 1 mg – 120 - 140 U
- **Dosage:** IV Bolus followed by continuous IV (e.g. 5000 to 10,000 U followed by 750 – 1000 U/hr continuous IV)
  - Not IM, SC may be used - haematoma

Heparin – ADRs and CI

- Bleeding – haematuria (first sign)
- Thrombocytopenia (HITT): abnormal antibodies activating platelets
- Transient reversible alopecia
- Osteoporosis
- Hypersensitivity – urticaria, rigor, fever anphylaxis

- **Contraindications:**
  - Bleeding disorders
  - Severe hypertension
  - SABE
  - Ocular and Neurosurgery
  - Cirrhosis and renal failure
  - Aspirin and other antiplatelet drugs

LMWH - Fractionated Heparin (MW – 3000 to 7000)

- Vs UFH: General: 1) Selective inhibition of Xa (little on IIa) **2)** No scaffolding action – bring together AT III and Iia **3)** Smaller effect on aPTT **4)** Lesser antiplatelet action and thrombocytopenia **5)** Lesser incidence of haemorrhage
  - Kinetics: Better SC bioavailability, half-life prolonged – once daily and no laboratory monitoring of aPTT required
- **Uses of Heparin:**
  - DVT and pulmonary embolism: venous thrombus are fibrin thrombi
  - Prophylaxis of DVT – surgery, stroke etc.
  - MI: Platelet thrombi - Heparin 2-8 days IV after coronary angioplasty and stent application
  - CVA: No value – can be devastating – may be used in cerebral embolism
  - Unstable angina: short term regime – with antiplatelet
  - To maintain patency of canula and shunts in dialysis patients
  - AF in RHD – mainly warfarin and aspirin –and also DIC

Protamine sulfate

- Strongly basic drug with low MW
- Source Fish sperm
- 1 mg neutralizes 100 U of heparin
- Administration needs judgment of heparin administered and metabolized
- Used infrequently – action of heparin disappears itself – whole blood transfusion
- Mainly used to terminate heparin action quickly – after cardiac surgery
- In heparin absence – itself is weak anticoagulant
- Releases histamine - hypersensitivity

Direct Thrombin Inhibitors

- Lepirudin: Recombinant preparation of Hirudin – Leech (*Hirudinaria granulosa*)
  - Injected IV in heparin induced thrombocytopenia
  - No antidote
- Bivalirudin and argatroban - similar

Remember: Heparin - X, II and AT III

Next Class – ORAL ANTICOAGULANTS

Khublei shibun/Thanks