Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI2) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A2 (TXA2), and serotonin (5-HT).
Clotting Cascade

Intrinsic Pathway
- XII
- XI
- IX
- VIII

Extrinsic Pathway
- Tissue Factor
- VII

Common Pathway
- Xa
- Va

- 24 hr half life
- 48 hr half life
- 60 hr half life

- Pro-II
- Thrombin IIa
- Fibrinogen (I)
- Fibrin
• Platelet-rich thrombi (white thrombi) form in the high flow rate arteries.

• Occlusive arterial thrombi cause serious disease by producing downstream ischemia of extremities or vital organs, and can result in limb amputation or organ failure.

• Venous clots tend to be more fibrin-rich, contain large numbers of trapped red blood cells, and are

• recognized pathologically as red thrombi. Deep venous thrombi (DVT) can cause severe swelling and pain of the affected extremity, but the most feared consequence is pulmonary embolism (PE).
Drug List

• **Anticoagulants**
  - Warfarin
  - Heparin
  - Low MW Heparins

• **Anti-platelet Drugs**
  - Aspirin
  - Ticlopidine
  - Dipyridamole
  - Abciximab, eptifibatide, tirofiban

• **Thrombolytic Drugs**
  - Streptokinase, Reteplase, Urokinase
Heparin

- Containing a mixture of sulfated mucopolysaccharides of various sizes
  - Unfractionated (5000-30000 Da)
  - Low molecular weight (LMWH) (1000-5000 Da)
The antithrombin-binding structure of heparin.
Heparin

- **Heparin** is the drug of choice for *parenteral* anticoagulant therapy
- **Mechanism:**
  - Heparin binds to antithrombin.
  - Heparin-antithrombin complex binds to and inactivates coagulation factors.
  - Heparin prolongs the aPTT.
Heparins do not affect thrombin bound to fibrin or Xa bound to platelets.

**MECHANISM OF HEPARIN ANTICOAGULANT EFFECT**

- Activated clotting factors: IX, X (II), XI, XII
- Thrombin

HEPARIN

- Low affinity for clotting factors

ANTITHROMBIN III

- High affinity for factors

ANITITHROMBIN III

- Factor X inactivated

ANTITHROMBIN III

- Factor X III
Routes of Administration

- Continuous IV
- Subcutaneous Minidose
  - for post-surgery prophylaxis
- NOT GIVEN IM
- NOT GIVEN ORAL
Heparin Pharmacokinetics

• Onset
  * I.V. immediate anticoagulant
  * S.C. begins in 20 - 30 minutes
  * Continuous IV infusion: 2 - 3 hour delay unless an initial bolus injection is administered

• Duration (of a single dose)
  * IV, 1 - 3 hours
  * S.C, 12-24 hours

• Termination: partly metabolized in liver, excreted in the urine.
Indications for Heparin Therapy

• **Prophylaxis** of postoperative thrombosis - s.c.
• Deep venous thrombosis and pulmonary embolism
• Disseminated Intravascular Coagulation (DIC)
• Heparin is used when **rapid onset** of anticoagulation is required.
• If prolonged anticoagulation is necessary, then replaced with oral anticoagulant, i.e. **warfarin**
Heparin Toxicity

- **Hemorrhage**: from inadvertent overdose or from undiagnosed disease,
- Hematoma at site of injection
- **Thrombocytopenia**

  Stop heparin and use thrombin inhibitor.
Heparin Toxicity

- Less common side effects:
  platelet aggregation, acute hypersensitivity, alopecia, osteoporosis.
Heparin Contraindications

• Any site of active or potential bleeding
• Severe hypertension or known vascular aneurysm
• Recent head, eye, or spinal cord surgery
• Head trauma
• Lumbar puncture or regional anesthetic block
• Tuberculosis, visceral carcinoma, GI ulcers
• Renal or liver diseases.
• Threatened abortion.
Monitoring Heparin Therapy

• aPTT (Activated Partial Thromboplastin Time) tested prior to starting therapy.

• aPTT of 1.5 - 2.0 times control is the typical therapeutic goal.
Treatment of Heparin Overdose

- Stop administration

- Protamine sulfate
  - binds to and inactivates heparin
  - must be given slowly IV
Low Molecular Weight Heparin

- Enoxaparin, Dalteparin, tinzaparin
- Smaller, active pieces of regular heparin
- Greater anti-Xa activity,
- Less anti-platelet activity
- Used (s.c. injection) for prophylaxis of DVT associated with hip and abdominal surgery
Low Molecular Weight Heparin

- Longer duration, higher bioavailability,
- Clotting tests not usually required (unless pregnancy, over weight, renal failure).
- Need lower doses.
- Not antagonized completely by protamine.
**Regular Heparin**

- Heparin
  - AT-III
  - Xa

**Low Molecular Weight Heparin**

- LMWH
  - AT-III
  - Xa

- Required binding site for factor IIa is not available on LMWH so IIa activity is not suppressed

- Anti-Xa: Anti-IIa activity = 2:1 to 4:1
Thrombin inhibitor

- **Hirudin**

- Medicinal leeches:
  - Used since ancient times.
    - Hirudin is the most potent natural inhibitor of thrombin.
    - Hirudin binds to and inhibits only the activity of thrombin.

- **Lepirudin** (recombinant)
  - administered parenterally and is monitored by the aPTT.
Oral direct thrombin inhibitors

- **Dabigatran etexilate mesylate** is the first oral direct thrombin inhibitor approved by the FDA.
- Dabigatran was approved to reduce risk of stroke and systemic embolism with nonvalvular atrial fibrillation.
- The oral bioavailability is 3–7% in normal volunteers.
- The half-life of the drug is 12–17 hours.
- Renal impairment results in prolonged drug clearance and may require dose adjustment;
- The drug should be avoided in patients with severe renal impairment.
- The primary toxicity of dabigatran is bleeding
Oral Anticoagulants: Warfarin

- **Coumarin**-type oral anticoagulants

- **Mechanism:**
  - Inhibits vitamin k-dependent posttranslation modification of clotting factors: thrombin, VII, IX, X, protein C and S
  - Without the $\gamma$ carboxylation the clotting factors are inactive.
Vitamin K - Dependent Clotting Factors

Synthesis of Functional Coagulation Factors

VII
IX
X
II
Warfarin: Pharmacokinetics

- **Onset:** considerably **delayed** (8-12 hours)
  - delay in onset is due to long t1/2 of warfarin and the fact that pre-existing clotting factors are slowly cleared from the blood (t1/2 for VII = 6 hours)
Warfarin: Pharmacokinetics

- **Distribution**:  
  - Rapid and complete absorption  
  - 99% bound to plasma albumin

- **Termination**: *delayed* (2 -5 days)  
  - Liver and kidney metabolism  
  - Long elimination t1/2
Warfarin: Toxicities and Contraindications

- **Hemorrhage**

- Anorexia, nausea, vomiting, diarrhea

- **Contraindications**
  - pregnancy: congenital abnormalities
  - Any recent bleeding
  - Severe hypertension or known vascular aneurysm
Warfarin: Indications

- **Overlap with heparin therapy to avoid long delay in onset of action**
- Deep venous thrombosis
- Pulmonary embolism
- Atrial fibrillation
- Mechanical and prosthetic heart valves
• **Warfarin is only given orally**
• Initial doses followed by maintenance doses
  • adjust according to PT time (INR)
• Determine **PT time**,  
  This will take a week to occur.
Monitoring Warfarin

- Therapeutic limits for oral anticoagulants is determined by:
  \[ \text{INR} = \]

**Individual patient variation is very high**
Due to differences in absorption, elimination, liver function, and drug-drug interactions.
Warfarin: Drug-drug Interactions

• Warfarin is a **classic example** for many types of drug-drug interaction
• Inhibition or acceleration of warfarin metabolism
• Displacement from plasma protein binding sites
• Interference with mechanism of action
• Interference with absorption
Interactions

• Pharmacokinetic

  - changes in the absorption, protein binding, and/or metabolism

  - metabolism/elimination via cytochrome P450 system (common)

  - displacement of warfarin from plasma protein-binding sites eg NSAIDs (less important)

• Pharmacodynamic

  - alter the risk of bleeding or clotting by either effect on platelet aggregation or vitamin K catabolism
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<th>Decreased Prothrombin Time</th>
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Oral Xa inhibitors

- **Ex: Rivaroxaban**

- Represent a *new class* of oral anticoagulant drugs that require no monitoring.

- Along with *oral direct thrombin inhibitors* these drugs are having a major impact on antithrombotic pharmacotherapy.

- These drugs are given as fixed doses and do not require monitoring.

- They have a rapid onset of action and shorter half-lives than warfarin.
Antiplatelet Drugs

• Platelets form initial hemostatic plug
• Platelets are associated with atherosclerotic plaque deposits and pathological thrombi.
• A key activator of platelet aggregation is Thromboxane A₂ (TXA₂)
• TXA₂ is a product of the arachidonic acid pathway that involves formation of prostaglandins by the enzyme cyclooxygenase
Anti-platelet Agents – Mechanism of action

Thrombin

- COX-1
- TBX A2

G IIb / IIIa R

ADP release

ADP

G IIb / IIIa R
Anti-platelet Agents – Mechanism of action

Thrombin → ADP → GP IIb / IIIa

Aspirin → COX-1 → TBX A2

Dipyridamole → cAMP

Clopidogrel

ADP release

G IIb / IIIa Inhibitors
Platelet

Cyclooxygenase

\[ \text{TXA}_2 \]

+++ platelet aggregation
+++ platelet shape change
+++ platelet granule release
+++ vasoconstriction

Aspirin

+++ low dose

+++ high dose

Endothelial cell

Cyclooxygenase

\[ \text{PGI}_2 \]

Inhibits platelet aggregation
Inhibits platelet secretion
+++ vasodilation
Aspirin: Antiplatelet Effects

- **Aspirin, at very low doses, irreversibly inhibits cyclooxygenase**
- Since platelets cannot synthesize new enzyme, aspirin inhibits TXA₂ formation and platelet aggregation for the life of the platelet (7-10 days).
Aspirin: Therapeutic Uses

- The FDA has approved the use of 325 mg/d aspirin for primary prophylaxis of.
- It should be administered routinely to virtually all patients with myocardial infarction.
- Secondary prevention of MI and stroke
- Primary prevention of cardiovascular disease (benefits less clear).
Adverse effects

• GI ulceration 6-31%
• Haemorrhage
• Bronchospasm
• Interstitial nephritis, papillary necrosis, proteinuria, renal failure
• Reye’s syndrome in children CI <16yrs
• Dangerous in overdose
Dipyridamole

• Increases Adenosine con. Coronary dilator.
• Increases coronary oxygen concentration.
• Phosphodiesteraz inhibitor (cAMP & cGMP rises) Antiplatelet effects.
• Little side effects:
  Headache, dizziness, flushing, GI, mialgia
Dipyridamole

• Indications:

• Dipyridamole by itself has little or no beneficial effect.

• In combination with aspirin to prevent cerebrovascular ischemia.

• In combination with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves.
Other Antiplatelet Drugs

• Ticlopidine, clopidogrel, and prasugrel
• These drugs irreversibly block the ADP receptor on platelets.
• The duration of the antiplatelet effect is 7–10 days
• AR: GI upset, Bleeding, Blood dyscrasias; leucopenia.
• Prodrugs, become active after the first pass effect.
Antiplatelet agents

**Glycoprotein IIb/IIIa inhibitors**

Abciximab, Eptifibatide,

– Because of their short half-lives, they must be given by continuous infusion.

○ Inhibit cross-bridging of platelets by fibrinogen.

– Abciximab is **Fab fragment of monoclonal antibody.**
Indications

• Greater antithrombotic activity than aspirin or heparin
• Approved as antithrombotic during angioplasty
• Approved for acute coronary syndromes
Thrombolytic Agents

- **Thrombolytic = fibrinolytic**
- **Normal fibrinolysis:**
  - Clots are dissolve by the action of the protease **plasmin**
  - Plasmin is formed from inactive plasminogen by **tissue plasminogen activator (tPA)**
  - tPA has much higher activity against fibrinogen bound to clots than free fibrinogen in circulation.
Therapeutic Objectives

- **Destroy formed pathological thrombus**
  - Dissolving preformed clots is difficult to achieve without causing bleeding, but fibrinolytic drugs like rtPA, reteplase, streptokinase can be used in special situations.
Thrombolytic Therapy

• **Indications**
  - Acute myocardial infarction (start before 6h)
  - Pulmonary embolism
  - Deep venous thrombosis
tPA (Alteplase & Reteplase)

• Plasminogen can also be activated endogenously by (t-PAs).

• These activators preferentially activate plasminogen that is bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus and avoids systemic activation.

• Reteplase is as effective as alteplase and have **simpler** dosing schemes because of its longer half-life.
Streptokinase

• A nonenzymatic activator of plasminogen extracted from hemolytic streptococci.
• A loading dose of streptokinase used to saturate pre-existing antibodies.
• Serious hemorrhage is a potential side effect
Urokinase

• Intrinsic compound
• Isolated from urine or renal cell cultures
• Non-antigenic
• Cleaves plasminogen
Indications of fibrinolytic

Administration of fibrinolytic drugs by the IV route is indicated in cases of:

• **pulmonary embolism**
• Severe deep venous thrombosis
• *Ascending thrombophlebitis of* femoral vein with severe lower extremity edema.
• Recombinant t-PA has also been approved for use in **acute ischemic stroke** within 3 hours of symptom onset.
• **These drugs are also given intra arterially**, especially for peripheral vascular disease.
Contraindications

• Aortic dissection
• Recent or active bleeding
• Recent major surgery
• Coagulation disorder
• Pregnancy
• Previous intracranial bleeding
Clotting deficiencies

- Vitamin K; Phytonadione (K1), Menakinone (K2)
  - Oral: 5 mg tablets
  - Slow IV injection
- IV administration of vitamin K1 should be slow, because rapid infusion can produce dyspnea, chest and back pain, and even death.
Indications

• Treating depression of prothrombin activity by excess warfarin or K deficiency

• Vitamin K1 is currently administered to all newborns to prevent hemorrhagic disease of vitamin K deficiency, which is especially common in premature infants.

• Vitamin K deficiency frequently occurs in hospitalized patients in ICU because of poor diet, parenteral nutrition, recent surgery, multiple antibiotic therapy, and uremia.
Clotting deficiencies

• Spontaneous bleeding occurs when factor activity is less than 5–10% of normal. Plasma fractions - for hemophilia
  • Antihemophilic factor (VIII,IX)
  • Parenteral
Clotting deficiencies

• Desmopressin acetate (DDAVP) increases the factor VIII activity of patients with mild hemophilia A or von Willebrand disease.
• It can be used in preparation for minor surgery without any requirement for infusion of clotting factors.
Drugs to stop bleeding

- Aminocaproic acid chemically similar to the lysine,
- It is a synthetic inhibitor of fibrinolysis.
- It competitively inhibits plasminogen.
- Tranexamic acid is an analog.

- It is rapidly absorbed orally and is cleared from the body by the kidney.
Clinical uses of EACA

• Adjunctive therapy in hemophilia,
• For bleeding from fibrinolytic therapy,
• Prophylaxis for rebleeding from intracranial Aneurysms.
• Treatment in patients with postsurgical Gastrointestinal bleeding and post prostatectomy bleeding and
• Bladder hemorrhage Secondary to radiation- and drug induced cystitis.
Adverse effects of the drug

- Intravascular thrombosis from inhibition of plasminogen activator, Hypotension, Myopathy, abdominal discomfort, diarrhea, and nasal stuffiness.
- The drug should not be used in patients with DIC or genitourinary bleeding of the upper tract, eg, kidney and ureters, because of the potential for excessive clotting
References

• Katzung; Basic and Clinical Pharmacology 13

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