Introductory Clinical Pharmacology

Chapter 43
Anticoagulant and Thrombolytic Drugs
Thrombosis

• Thrombus

• Arterial thrombosis
  – Begins with platelet adhesion to arterial wall
  – Platelets release ADP and TXA2
  – Addition platelets attracted to evolving thrombus
  – Coagulation cascade initiated with occlusion of vessel

• Venous thrombosis
  – Develop where blood flow is slowed
  – Blood stagnation initiates clotting cascade
  – Typical venous thrombus has a long tail
Clotting Cascade

• Stage one
  – Formation of a platelet plug
    • Platelet aggregation
    • Formation of fibrinogen bridges

• Stage two
  – Coagulation
    • Production of fibrin
Spasm in damaged smooth muscle

Injury

Platelet aggregation and adhesion

1. VASCULAR PHASE

2. PLATELET PHASE

COMMON PATHWAY

INTRINSIC PATHWAY

Extrinsic Pathway

Prothrombin

Thrombin

Tissue thromboplastin

Fibrinogen

Platelet thromboplastin

Clotting factors VIII, IX, X, XI, XII

Fibrin

Ca^{2+}

Platelet factors

Tissue factors

Clotting factor VII

Plasminogen

Ca^{2+}

Plasmin

3. COAGULATION PHASE

Activation of clotting system and clot formation

4. CLOT RETRACTION

Contraction of blood clot

5. CLOT DESTRUCTION

Enzymatic destruction of clot
Anticoagulants

- Three classes of drugs used to treat or prevent thrombus formation
  - Anticoagulants
  - Antiplatelet
  - Thrombolytic
- Do not “thin” blood
- Do not lyse existing clots
- Do prevent new clot formation
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prototype</th>
<th>Drug Action</th>
<th>Therapeutic Effect</th>
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<tbody>
<tr>
<td>Anticoagulant:</td>
<td>Heparin</td>
<td>D</td>
<td>Prevention of P</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic</td>
<td>Streptokinase</td>
<td></td>
<td>Removal of P</td>
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</table>

**Notes:**
- D: Decrease
- P: Prevention
Antiplatelet Drugs

- Suppress platelet aggregation
- Platelet core forms the bulk of an arterial thrombus
- Used in the prevention of arterial thrombus formation
- Three major groups
  - Aspirin
  - ADP receptor antagonists
  - GPIIb/IIIa antagonists
Antiplatelet Drugs: Actions and Uses

- **Aspirin**: Prohibits aggregation of platelets for lifetime of platelet
- **ADP blockers**: Alter cell membrane preventing aggregation
- **Glycoprotein receptor blockers**: Prevent enzyme production; inhibit platelet aggregation
- **Antiplatelet drug therapy**: Treats acute coronary syndrome, myocardial infarction, stroke, and intermittent claudication
Aspirin

- Causes irreversible inhibition of cyclooxygenase
- TXA2
  - Promotes platelet activation
  - Acts on vascular smooth muscle to promote vasoconstriction

- Indications
  - Primary prevention of MI
  - Secondary prevention of MI
  - Prevention of stroke in pts with a history of TIA

- Adverse Effects
  - Increased risk of GI bleed and hemorrhagic stroke
ADP Receptor antagonists

• Ticlopidine

• Clopidogrel

• Cause irreversible blockade of ADP receptors on platelet surface to prevent ADP stimulated aggregation

• Uses: Ticlopidine (Ticlid): prevention of thrombotic stroke Clopidogrel (Plavix): reduce risk of thrombotic events: MI, ischemic stroke, vascular death

• Adverse effects: Ticlid: life-threatening hematologic reactions including neutropenia, agranulocytosis, thrombotic thrombocytopenia purpura. Plavix: similar to aspirin: abd pain, dyspepsia, diarrhea, rash.
GPIIb/IIIa

- Most effective antiplatelet drugs on the market
- Three available: abciximab, tirofiban, eptifibatide.
- Cause reversible blockade of platelet GPII/IIIa receptors
- Use: ACS and pts undergoing percutaneous coronary intervention
Other antiplatelet drugs

- Dipyridamole (persantine)
  - Suppresses platelet aggregation by increasing plasma levels of adenosine
  - Prevention of thromboembolism following heart valve replacement surgery in combination with warfarin

- Aggrenox  dipyridamole+aspirin
  - Uses: prevent recurrent ischemic stroke in pts with previous CVA or TIA
Antiplatelet Drugs: Contraindications and Precautions

• Contraindicated in patients with:
  – Known hypersensitivity to the drug, congestive heart failure, active bleeding, thrombotic thrombocytopenic purpura
  – During pregnancy and lactation

• Used cautiously in elderly patients, pancytopenic patients, those with renal and hepatic impairment
Oral and Parenteral Anticoagulants

- Anticoagulants: Prevent the formation and extension of a thrombus
- Warfarin: Oral anticoagulant
- Low–molecular-weight heparins (LMWH)
  - Produce stable responses when administered at recommended dosages
  - Bleeding less likely to occur
# Antiplatelet Drugs: Interactions

<table>
<thead>
<tr>
<th>Interactant drug</th>
<th>Effect of interaction</th>
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</thead>
<tbody>
<tr>
<td>Aspirin and NSAIDs</td>
<td>Increased risk for bleeding</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Increased effectiveness of anti-infective</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decreased digoxin serum</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increased phenytoin serum</td>
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</table>
Warfarin

- Only oral anticoagulant available in the US
- Acts as an antagonist of vitamin K
- Blocks synthesis of Factors VII, IX, X and prothrombin
- Uses: long term prophylaxis of thrombosis
  - Prevention of thrombosis and associated PE
  - Prevention of thrombosis in pts with prosthetic heart valves
  - Prevention of thrombosis in patients with atrial fibrillation
Warfarin

• Monitoring
  – Prothrombin time (PT)
  – International normalized ratio (INR)

• Antidote
  – Vitamin K

• Adverse Effects
  – Bleeding, fetal hemorrhage and teratogenesis
Parenteral Anticoagulants: Actions

Heparin

- Inhibits formation of fibrin clots
- Inhibits conversion of fibrinogen to fibrin
- Inactivates factors necessary for clotting of blood

• LMWHs: Inhibits clotting reactions by binding to antithrombin III
Heparin

- Rapid acting anticoagulant
- Administered only by injection
- A mixture of long polysaccharide chains
- Helps antithrombin inactivate clotting factors
- Uses: pulmonary embolism, evolving stroke, massive DVT, open heart surgery, dialysis, prevention of post-operative venous thrombosis, DIC, MI
- Adverse Effects: Bleeding, thrombocytopenia, hypersensitivity reactions
- Monitoring: PTT
- Antagonist: Protamine sulfate
Low Molecular Weight Heparin

- Enoxaparin (Lovenox), dalteparin (Fragmin), tinzaparin (Innohep)
- Composed of molecules that are shorter than in unfractionated heparin
- Administered on a fixed dose schedule
- Do not require PTT monitoring
- First line therapy for prevention and treatment of DVT
- Prefentially inactivate factor Xa
- Adverse effects: severe neurologic injury, immune-mediated thrombocytopenia, bleeding
Oral and Parenteral Anticoagulants: Contraindications

- Contraindicated in patients with:
  - Known hypersensitivity to drugs, active bleeding, hemorrhagic disease, tuberculosis, leukemia, uncontrolled hypertension, gastrointestinal (GI) ulcers, recent surgery of the eye or central nervous system (CNS), aneurysms, severe renal, hepatic disease; during lactation
Oral and Parenteral Anticoagulants: Interactions
Oral and Parenteral Anticoagulants: Interactions (cont’d)

<table>
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<th>Interactant drug</th>
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<tr>
<td>Beta blockers, loop diuretics</td>
<td>I</td>
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</table>
Thrombolytic Drugs: Actions

- Breaks down fibrin clots by converting plasminogen to plasmin
- Plasmin: Enzyme that breaks down fibrin of blood clot
  - Reopens blood vessels after occlusion and prevents tissue necrosis
Thrombolytic Drugs: Uses

- Used to treat:
  - Acute myocardial infarction by lysis of blood clots in coronary arteries
  - Blood clots causing pulmonary emboli and DVT
  - Blood clots causing pulmonary emboli and DVT
Thrombolytic Drugs: Adverse Reactions

- **Bleeding**
  - Internal bleeding: GI tract, genitourinary tract, brain
  - External bleeding: Broken skin, such as venipuncture sites and recent surgical wounds

- **Allergic reactions**
Thrombolytic Drugs: Contraindications and Precautions

- Contraindicated in patients with hypersensitivity, active bleeding, history of stroke, aneurysm, recent intracranial surgery

- Used cautiously in patients:
  - Who have recently undergone major surgery
  - With hypertension, diabetic retinopathy, or any condition with bleeding a significant possibility
  - Currently receiving oral anticoagulants
Thrombolytic Drugs: Interactions

- Increased risk for bleeding when coadministered with medications that prevent blood clots, or with an anticoagulant
Nursing Process: Assessment

- Preadministration assessment
  - Obtain drug history and vital signs
  - Examine extremity for color and skin temperature
  - Check for pedal pulses, noting rate and strength of pulses
  - Note areas of redness or tenderness and ask patient to describe current symptoms
  - Complete blood count
Nursing Process: Assessment

- Ongoing assessment
  - Assess patient for signs of bleeding and hemorrhage
  - Monitor for intracranial bleeding by assessing level of consciousness
  - Monitor PT/INR results
  - Monitor for any indication of hypersensitivity reaction
Nursing Process: Planning

- Expected outcome
  - Optimal response to therapy
  - Support of patient needs related to management of adverse reactions
  - Understanding of post-discharge drug regimen
Nursing Process: Implementation

- Promoting an optimal response to therapy
  - Oral administration of anticoagulants

- Check prothrombin flow sheet; review PT/INR results

- For rapid anticoagulation: Loading dose of heparin, followed by maintenance dose of warfarin based on PT or INR
Nursing Process: Implementation

• Promoting an optimal response to therapy (cont’d)
  – Parenteral administration of anticoagulants
    • Administration of heparin: Intermittent IV, continuous IV infusion, or SC route
    • Inspect needle site for signs of inflammation, pain, and tenderness along pathway of vein
    • Closely monitor blood coagulation tests, complete blood count, platelet, and stool analysis
Nursing Process: Implementation

- Administration of thrombolytics
  - Assess patient for bleeding until therapy is completed; vital signs
  - Administer opioid analgesic for pain management

- Drugs used to maintain IV patency
  - Inspect needle site
  - Avoid using excessive pressure when the drug is injected into the catheter
Nursing Process: Implementation

- Monitoring and managing patient needs
  - Risk for injury
  - Check for signs of bleeding: Drop in blood pressure, rise in pulse rate, urine, stool; visually check nasogastric suction; check toothbrush, gums after oral care
Nursing Process: Implementation

• Monitoring and managing patient needs (cont’d)
  - Individual effective therapeutic regimen management
  - Educate about food and drug interactions
  - Instruct patient to wear medical identification to indicate receiving anticoagulant or antiplatelet therapy
Nursing Process: Implementation

• Monitoring and managing patient needs (cont’d)
  
  – Anxiety
    
    • Reassure patient and communicate with family member
    
    • Assess for signs of bleeding and hemorrhage
    
    • Monitor vital signs and for signs of allergic reactions
Nursing Process: Implementation

• Managing anticoagulant overdosage
  – Oral anticoagulants
    • Monitor for symptoms of warfarin overdosage: blood in stool; petechiae; oozing from superficial injuries; excessive menstrual bleeding
Managing anticoagulant overdosage (cont’d)

- Parenteral anticoagulant
  - After administration of heparin: Monitor blood pressure and pulse rate
  - Observe new evidence of bleeding until blood coagulation tests are within normal limits
  - Blood transfusions or fresh frozen plasma may be ordered
Nursing Process: Implementation

- Educating the patient and family
  - Provide full explanation of the drug regimen, possible adverse reactions, and signs of bleeding tendencies
  - Explain the importance of monitoring PT or INR
  - Explain the importance of avoiding taking drugs or changing brands of anticoagulants without informing primary health care provider
Nursing Process: Implementation

- Educating the patient and family (cont’d)
  - Advise the patient to inform dentist or primary health care providers of therapy with this drug before any treatment
  - Explain the importance of taking the drug at the same time each day
  - Instruct the patient to avoid alcohol unless approved by primary health care provider
  - Provide dietary information
Nursing Process: Implementation

- Educating the patient and family (cont’d)
  - Explain the necessity of contacting the primary health care provider immediately if evidence of bleeding occurs
  - Importance for women of childbearing age to use reliable contraceptive to prevent pregnancy
  - Importance of wearing or carrying medical identification
Nursing Process: Evaluation

- Therapeutic drug effect is achieved
- Adverse reactions are identified, reported, and managed successfully
- Patient demonstrates understanding of drug regimen
- Patient verbalizes importance of complying with prescribed therapeutic regimen
- Patient lists or describes early signs of bleeding
- Patient verbalizes an appropriate diet.