DRUGS USED IN COAGULATION DISORDERS

Course:
Integrated Therapeutics 1

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Materials on:
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Required reading:
Katzung, Chapter 34
DISORDERS OF COAGULATION

Types of coagulation disorders

– Excessive thrombosis
  • A **thrombus** is a blood clot that forms inside a blood vessel or cavity of the heart
  • An **embolus** is a blood clot that moves through the bloodstream until it lodges in a narrowed vessel and blocks circulation
  • Arterial thrombi cause downstream ischemia of extremities or vital organs – may result in amputation or vital organ failure
  • Venous thrombi can cause embolism (pulmonary embolism), and pain and severe swelling of the affected tissue

– Excessive bleeding
  • Increased bleeding due to vascular injury
  • Bleeding from mucosal sites
  • Internal bleeding into deep tissues
TYPES OF BLOOD CLOTS

All clots involve both platelets and fibrin, but the degree of involvement of platelet/fibrin in thrombus formation depends on the vascular location

• **White (platelet-rich) thrombus**
  – Forms in high-pressure arteries and is the result of platelet binding to damaged endothelium and aggregation with little involvement of fibrin
  – Pathologic condition associated with white thrombi: local ischemia due to arterial occlusion (in coronary arteries: myocardial infarction / unstable angina)

• **Red thrombus (fibrin-rich with trapped RBCs)**
TYPES OF BLOOD CLOTS

All clots involve both platelets and fibrin, but the degree of involvement of platelet/fibrin in thrombus formation depends on the vascular location

- **White** (platelet-rich) thrombus
- **Red thrombus** (fibrin-rich with trapped RBCs)
  - Forms in low-pressure veins and in the heart; result of platelet binding and aggregation followed by formation of bulky fibrin tails in which red blood cells become enmeshed
  - Pathologic condition associated with red thrombi: embolism and distal pathology (deep vein thrombosis resulting in pulmonary emboli; cardiogenic emboli resulting in embolic stroke)
Scanning electron microphotograph of evolving red thrombus
CATEGORIES OF DRUGS USED IN COAGULATION DISORDERS

Drugs used in thromboembolic disorders

- **Anticoagulants** – regulate the function and synthesis of clotting factors
  - Primarily used to prevent clots from forming in the venous system and heart (red thrombi)
- **Antiplatelet drugs** – inhibit platelet function
  - Primarily used to prevent clots from forming in the arteries (white thrombi)
- **Thrombolytics** – destroy blood clots after they are formed
  - Re-establish blood flow through vessels once clots have formed

Drugs used in bleeding disorders
CATEGORIES OF DRUGS USED IN THROMBOEMBOLIC DISORDERS

Thrombus formation at the site of the damaged vascular wall
CATEGORIES OF DRUGS USED IN THROMBOEMBOLIC DISORDERS

Anticoagulants
CATEGORIES OF DRUGS USED IN THROMBOEMBOLIC DISORDERS

- **Anticoagulants**
- **Antiplatelet drugs**
CATEGORIES OF DRUGS USED IN THROMBOEMBOLIC DISORDERS

Anticoagulants

Antiplatelet drugs

Thrombolytics

Anticoagulants
ANTICOAGULANTS

• Parenteral anticoagulants
  – Indirect thrombin inhibitors
    • Heparin preparations
  – Direct thrombin inhibitors (DTIs)
    • Hirudin
    • Lepirudin
    • Bivalirudin
    • Argatroban

• Oral anticoagulants
  – Warfarin
PARENTERAL ANTICOAGULANTS

Heparin preparations

• Heparin sodium – unfractionated heparin (UFH, combination of low and high molecular weights, purified from animal sources); higher activity
• Enoxaparin, Tinzaparin – low molecular weight heparins (LMW); lower activity
• Fondaparinux – synthetic pentasaccharide
Heparin – mechanism of action

- Indirect thrombin inhibitor – binds plasma serine protease inhibitor antithrombin and increases its activity by 1000-fold
- Direct binding to thrombin, factors IX, X, XI, and XII in the intrinsic system, and inhibition of their activity
HEPARIN

Heparin – mechanism of action (continued)

- **Antiplatelet action** – heparin binding to thrombin inhibits thrombin-platelet interaction, and prevents platelet activation
- **Binding to endothelium and leukocytes** prevents leukocyte-leukocyte, leukocyte-platelet, and leukocyte-endothelial adhesion
HEPARIN

Heparin – clinical use

• Very hydrophilic; must be given IV or SC
• Used to treat disorders secondary to red (fibrin-rich) thrombi and reduce the risk of emboli
  – Protects against embolic stroke, pulmonary emboli
  – Administer to patients with deep vein thrombosis, atrial arrhythmias and other conditions that predispose towards red thrombi
  – Prevention of emboli during surgery or in hospitalized patients (reduces risk of emboli)
  – Heparin locks: prevents clots from forming in catheters
HEPARIN

- Adverse effects
  - Bleeding
  - Heparin-induced thrombocytopenia (HIT)
    - Mechanism: immunogenicity of the complex of heparin with platelet factor 4 (PF4)
HEPARIN

• Adverse effects
  – Heparin-induced thrombocytopenia (continued)
    • A systemic hypercoagulable state
    • Characterized by venous and arterial thrombosis
    • Related to the immune response to heparin
    • Treatment: to discontinue heparin and administer DTI or Fondaparinux
HEPARIN

- **Contraindications**
  - Severe hypertension
  - Active tuberculosis
  - Ulcers of GI tract
  - Patients with recent surgeries

- **Reversal of heparin action**
  - Protamine sulfate (will not reverse the action of Fondaparinux)
DIRECT THROMBIN INHIBITORS

Mechanism of action – direct inhibition of the protease activity of thrombin

- Bivalent direct thrombin inhibitors (bind at both active site and substrate recognition site)
  - Hirudin
  - Lepirudin
- Inhibitors binding only at the thrombin active site
  - Argatroban
DIRECT THROMBIN INHIBITORS

- **Hirudin** – purified from medicinal leeches
- **Lepirudin** – recombinant form of this protein
  - Should be used with great caution – no antidote exists
  - Used in heparin-induced thrombocytopenia
  - Repeated use may cause anaphylactic reaction
- **Argatroban** – small molecular weight inhibitor
  - Used in coronary angioplasty and heparin-induced angioplasty
  - Short-acting drug – used intravenously

Adverse effects of direct thrombin inhibitors (DTI)
- All DTI’s may cause bleeding
ORAL ANTICOAGULANTS

Warfarin – the most commonly prescribed anticoagulant in U.S.

- **Mechanism of action**
  - Inhibits reactivation of vitamin K, by inhibiting enzyme vit K epoxide reductase
  - Inhibits carboxylation of glutamate residues by GGCX (γ-glutamyl carboxylase) in prothrombin and factors VII, IX, and X, making them inactive

- **Two stereoisomers: R and S**
  - S-isomer is 3 to 5-fold more potent
ORAL ANTICOAGULANTS

• Warfarin – Mechanism of action

VKOC1 – vit K epoxide reductase complex subunit 1
GGCX - γ-glutamyl carboxylase
CALU – calumenin

Proteins affected by carboxylation
Factor II (prothrombin)
Factors VII-X (intrinsic hemostatic factors)

Other proteins that function in apoptosis, bone ossification, extracellular matrix formation, etc.
ORAL ANTICOAGULANTS

- **Warfarin** – Pharmacokinetics
  - R-warfarin is metabolized by CYP3A4, and some other CYP isoforms
  - S-warfarin is metabolized primarily by CYP2C9
  - OH-derivatives are pumped out of hepatocytes by ABCB1 transporter into bile, excreted with bile
• Warfarin – Pharmacokinetics (continued)
  – Administered orally
  – Has 100% bioavailability
  – Delayed onset of action (12 h)
  – Long half-life (36 hr)
  – 99% of it is bound to plasma albumin
ORAL ANTICOAGULANTS

Warfarin

• Clinical use
  – Used to prevent thrombosis or prevent/treat thromboembolism
  – Atrial fibrillation
  – Prosthetic heart valves
  – Deep venous thrombosis

• Adverse effects
  – Teratogenic effect (bleeding disorder in fetus, abnormal bone formation)
  – Skin necrosis, infarction of breasts, intestines, extremities
  – Osteoporosis
  – Bleeding
ORAL ANTICOAGULANTS

Warfarin

• Narrow therapeutic window
• FDA estimates that 2 million patients start taking warfarin every year in U.S.
• Warfarin is second most common drug (after insulin) implicated in emergency room visits for adverse effects
• Correct warfarin dose varies widely from patient to patient
  – Significant individual variability based on disease states and genetic make-up
  – Multiple drug interactions
ORAL ANTICOAGULANTS

- Warfarin dose is titrated based on laboratory testing
  - Prothrombin time (PT) – time to coagulation of plasma after the addition of a Tissue Factor (TF, or Factor III) – used for the evaluation of the extrinsic pathway
  - International normalized ratio (INR)
    - 0.9-1.3 – normal
    - 0.5 – high chance of thrombosis
    - 4.0-5.0 – high chance of bleeding
    - 2.0-3.0 – range for patients on warfarin
Individual variability in the action of warfarin

- Pharmacogenomics of warfarin
  - VKORC1 (vit K epoxide reductase complex subunit 1) – responsible for 30% variation in dose (low and high dose haplotypes),
    - High dose haplotype is more common in African Americans, they are more resistant to warfarin
    - Low dose haplotype is more common in Asian American patients, they are less resistant to warfarin
ORAL ANTICOAGULANTS

Individual variability in the action of warfarin

• Pharmacogenomics of warfarin (continued)
  – CYP2C9 – responsible for 10% variation in dose, mainly among Caucasian patients
  – Calumenin – endogenous endoplasmic reticulum protein inhibitor of GGCX (carboxylase enzyme)
  – FDA now encourages health professionals to test patients for their polymorphisms in these specific genes, to determine an effective and safe dose – kits are now available

• Effect of disease states
  – Hyperthyroidism patients will require lower doses, while hypothyroid patients are more resistant to warfarin
ORAL ANTICOAGULANTS

Warfarin drug interactions

• Pharmacokinetic interactions
  – CYP enzyme induction
  – CYP enzyme inhibition
  – Reduced plasma protein binding

• Pharmacodynamic interactions
  – Synergism with other antithrombotic drugs
  – Reduced clotting factor synthesis (in liver diseases)
  – Competitive antagonism (vit K)
  – Clotting factor concentration (diuretics)
**ORAL ANTICOAGULANTS**

Pharmacokinetic and pharmacodynamic drug and body interactions with warfarin

<table>
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<th>Increased Prothrombin Time</th>
<th>Decreased Prothrombin Time</th>
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<td><strong>Pharmacokinetic</strong></td>
<td><strong>Pharmacodynamic</strong></td>
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<td>Drugs</td>
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<tr>
<td>Cimetidine</td>
<td>Aspirin (high doses)</td>
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<tr>
<td>Disulfiram</td>
<td>Cephalosporins, third-generation</td>
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<tr>
<td>Metronidazole(^1)</td>
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<tr>
<td>Fluconazole(^1)</td>
<td><strong>Other factors</strong></td>
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<tr>
<td>Phenylbutazone(^1)</td>
<td>Hepatic disease</td>
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<tr>
<td>Sulfinpyrazone(^1)</td>
<td>Hyperthyroidism</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole</td>
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</tbody>
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\(^1\)Stereoselectively inhibits the oxidative metabolism of the (S)-warfarin enantiomorph of racemic warfarin.

**Reversal of warfarin action**

• Vitamin K, fresh-frozen plasma
ANTIPLATELET DRUGS

• Categories of antiplatelet drugs
  – Inhibitors of thromboxane $A_2$ synthesis
    • Aspirin (acetylsalicylic acid)
  – ADP Receptor Blockers
    • Clopidogrel
    • Ticlopidine
  – Platelet glycoprotein receptor blockers
    • Abciximab
    • Eptifibatide
    • Tirofiban
ANTIPLATELET DRUGS

Aspirin

- Mechanism of action – inhibition of cyclooxygenase 1
- Clinical use
  - Prevent heart attacks/acute myocardial infarction
  - Arterial thrombosis of the limbs resulting in intermittent claudication
  - Ischemic stroke
- Adverse effects
  - Peptic ulcer
  - GI bleeding
USE OF ASPIRIN FOR THE PREVENTION OF ACUTE MYOCARDIAL INFARCTION

Aspirin: prevents coronary occlusion or re-occlusion due to clot formation:

• Protects against heart attack in individuals with angina pectoris
• When taken at the time of or after a heart attack (160 mg), aspirin increases survival and reduces the risk of another heart attack
• Aspirin reduces the risk of thrombotic stroke
• Risk for severe bleeding prevents systematic use of aspirin by low-risk individuals
• When administered prophylactically, should be taken at lowest dose possible (75 -150 mg/day)
ANTIPLATELET DRUGS

Clopidogrel
Ticlopidine

- Mechanism of action – irreversibly block ADP receptors
- Clinical use
  - Prevention of arterial thrombosis in myocardial ischemia and stroke patients
  - Prevention of thrombosis in patients undergoing coronary stent surgery

Inhibition of ADP-induced platelet aggregation
ANTIPLATELET DRUGS

Pharmacogenomics of Clopidogrel

- High variability of Clopidogrel action
- Related primarily to metabolism by CYP2C19 isoenzyme
- Nonfunctional CYP2C19 allele is present in 50% Chinese, 34% African Americans, 25% Caucasians, and 19% Mexican Americans
- FDA Boxed warning (March 2010)
ANTIPLATELET DRUGS

Clopidogrel
Ticlopidine

• Adverse effects
  – Ticlopidine
    • Thrombotic thombocytopenic purpura
    • GI: nausea, dispepsia, diarrhea
    • Bleeding
    • Leukopenia
  – Clopidogrel
    • Less side effects that ticlopidine – is a preferred drug over ticlopidine
ANTIPLATELET DRUGS

Platelet glycoprotein (GP) receptor antagonists

- **Abciximab** – Anti-GPIIb/IIIa antibody
- **Tirofiban, Eptifibatide** – GPIIb/IIIa Antagonists

**Mechanism of action**
- Antagonize receptors on platelet cell membranes to prevent physical interaction of platelets with fibrinogen; inhibit platelet aggregation

Platelet GP (glycoprotein) IIb/IIIa receptor for fibrinogen, vitronectin, fibronectin, von Willebrand factor
ANTIPLATELET DRUGS

Platelet glycoprotein (GP) receptor antagonists
• Abciximab – Anti-GPIIb/IIIa antibody
• Tirofiban, Eptifibatide – GPIIb/IIIa Antagonists
• Clinical use
  – Prevention of thrombosis in unstable angina, other acute coronary syndromes and percutaneous coronary angioplasty

Platelet GP (glycoprotein) IIb/IIIa receptor for fibrinogen, vitronectin, fibronectin, von Willebrand factor
THROMBOLYTIC (FIBRINOLYTIC) DRUGS

- Induce fibrinolysis (lyse fibrin in thrombi after they have formed)
- General mechanism: activate endogenous fibrinolytic system by different mechanisms
**THROMBOLYTIC (FIBRINOLYTIC) DRUGS**

Plasminogen – plasma zymogen that forms active enzyme upon cleavage of the peptide bond between Arg-560 and Val-561 by tPA or uPA

Plasmin – active serine protease that cleaves and degrades fibrin and other proteins (fibronectin, laminin, thrombospondin, vWf)
THROMBOLYTIC (FIBRINOLYTIC) DRUGS

Types of fibrinolytic drugs (they all activate plasmin)

- **Tissue-type plasminogen activator (tPA)** – endogenous protein that cleaves plasminogen, released by endothelium, needs fibrin as coactivator.
- **Urokinase-type plasminogen activator (urokinase, uPA)** – endogenous protein, produced in kidneys; a human enzyme directly converting plasminogen to plasmin.
- **Streptokinase** – protein released by β-hemolytic Streptococci, forms the complex with plasminogen, converts it into plasmin by non-proteolytic mechanism.
FIBRINOLYTIC DRUGS

• tPA: Tissue-type Plasminogen Activator drugs
  • Alteplase (Activase): recombinant human protein
  • Reteplase: recombinant modified human protein
  • Tenecteplase: recombinant mutated human protein
• uPA: urokinase-type Plasminogen Activator
  • Urokinase
• Streptokinase preparations
  • Streptokinase (Streptase): purified from bacteria
  • Anistreplase, a complex of purified human plasminogen and bacterial streptokinase
FIBRINOLYTIC DRUGS

• Clinical uses
  • Embolic/thrombotic stroke
  • Acute myocardial infarction
  • Pulmonary embolism
  • Deep venous thrombosis
  • Ascending thrombophlebitis

Before t-PA  After t-PA

Clot in cerebral artery – stroke

• Treat with t-PA to break down the clot and open up artery
• Most effective within 3 hrs after embolic and thrombotic stroke
• Can exacerbate the damage produced by hemorrhagic stroke
FIBRINOLYTIC DRUGS

Adverse effects

• Bleeding from the systemic fibrinogenolysis (streptokinase, urokinase)
• Allergic reactions (streptokinase)

Systemic fibrinogenolysis with Streptokinase

Streptokinase, Urokinase

tPA
CATEGORIES OF DRUGS USED IN COAGULATION DISORDERS

Drugs used in thromboembolic disorders
• Anticoagulants
• Antiplatelet drugs
• Thrombolytics

Drugs used in bleeding disorders
• Inhibitors of fibrinolysis
  – Aminocaproic acid
  – Aprotinin
• Vitamin K
• Protamine – reverses effects of heparin
INHIBITORS OF FIBRINOLYSIS

Aminocaproic acid

• **Mechanism of action**
  – Structurally similar to amino acid lysine
  – Plasminogen binds to arginine and lysine residues on fibrinogen
  – Aminocaproic acid inhibits binding and activation of plasminogen into plasmin

• **Clinical indications**
  – Hemophilia
  – Bleeding from thrombolytic therapy
  – Prevention of bleeding from intracranial aneurysms
  – Post-surgery bleeding

• **Adverse effects**
  – Intravascular thrombosis
INHIBITORS OF FIBRINOLYSIS

Aprotinin

• Serine protease inhibitor – inhibits fibrinolysis by plasmin

• Used to reduce bleeding from surgery, especially involving extracorporeal circulation (open heart surgery, liver transplant)

• Adverse effects
  – Intravascular thrombosis – myocardial infarction, stroke
  – Renal damage
  – Anaphylactic reaction
OTHER PROCOAGULANT DRUGS

Vitamin K

• Induces activity of prothrombin and factors VII, IX, X (postranslational modification – carboxylation)
• Synthesized by bacterial flora in human intestine
• Antagonist of an oral anticoagulant warfarin
• Clinical uses
  – Overdose of warfarin
  – In newborns (especially prematurely born infants), and other cases of vitamin K deficiency
Protamine

- Antagonist of parenteral anticoagulant heparin
- Highly basic peptide that reacts with negatively charged heparin forming a stable complex with no anticoagulant activity
- Will not reverse the activity of fondaparinux
- Inactivation of LMW heparin preparations is incomplete