Blood Thinner Agent

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Outline:

- Blood thinner agent definition.
- Anticoagulants drugs.
- Thrombolytics.
Blood thinner agent

- Therapeutic interference with the clotting mechanism of the blood to prevent or treat thrombosis and embolism.
- Reducing the formation of blood clots in arteries and veins.
Pathophysiology of Hemostasis

- **Hemostasis** is a process which causes bleeding to stop, meaning to keep blood within a damaged blood vessel.
- Thrombosis is the most common abnormality of hemostasis; that is the formation of unwanted clot within a blood vessel.
- **Thrombotic disorders include:**
  - Acute myocardial infarction (arterial)
  - Acute ischemic stroke (arterial)
  - Pulmonary embolism (arterial)
  - Deep venous thrombosis (venous)

These disorders are treated with **anticoagulants** and **fibrinolytics**.
Classes of Drugs affect Thrombotic disorders

- **Prevent coagulation:**
  Drugs used to prevent unwanted blood clots developing and used as primary prevention or secondary prevention as Antiplatelet drugs.

- **Stabilize existing blood clots:**
  Cause stabilize for clot and will not dissolve a formed clot but prevent its propagation and growth as anticoagulants drugs.

- **Dissolve existing blood clots:**
  restore circulation patency more quickly by dissolving the existing clot as Thrombolytics drug.
anticoagulants drugs
1- Warfarin (Coumarin)

- Warfarin have been the main oral anticoagulant for more than 50 years.

- Its anticoagulant effect is not immediate, until those circulating clotting factors are cleared (5 hr for factor V and 2-3 days for factor II; thrombin).

- **Mechanism of action:**
  Warfarin inhibit Vit K 2,3 epoxide reductase and possibly Vit K quinone reductase, so prevent Vit K-dependent clotting factors to be activated (II, VII, IX, X and Prot C).
1- Warfarin (Coumarin)

- **Therapeutic Uses:**

  *It is used for chronic anticoagulation,*

  1. To prevent progression or recurrence of deep venous thrombosis “DVT” or pulmonary embolism after initial heparin therapy.

  2. Prophylactic in patients with; prosthetic heart valve or atrial fibrillation “AF”.
1- Warfarin (Coumarin)

- **Adverse effects:**
  1. Bleeding disorders
     - Minor bleeding can be treated with stopping warfarin and giving oral Vit K (2.5-5 mg).
     - Major bleeding need larger doses of Vit K (IV 5-10 mg) along with whole blood/fresh frozen plasma or plasma concentrates.
  2. Skin necrosis is rare, ‘women primarily’
  3. Purple toe syndrome; painful blue discoloration of the toe.

*It is contraindicated during pregnancy, since it is teratogenic/abortifacient.*
1- Warfarin (Coumarin)

- **Warfarin-related Drug Interactions:**

<table>
<thead>
<tr>
<th>Potentiating Anticoagulant activity</th>
<th>Antagonizing Anticoagulant activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td><strong>Factors</strong></td>
</tr>
<tr>
<td>Alcohol (acute intoxication)</td>
<td>Fever</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Stress</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Cancer</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Napoxen</td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td>Heparin</td>
<td>Vit K deficiency</td>
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<tr>
<td>Cephalosporin</td>
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<td>Erythromycin</td>
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<td>INH</td>
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<td>Ketoconazole</td>
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<td>Fluconazole</td>
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<td>Metronidazole</td>
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<tr>
<td>Omeprazole</td>
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<tr>
<td>Oral hypoglycemics</td>
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</tbody>
</table>
1- Warfarin (Coumarin)

- **Laboratory Monitoring:**
  - **Prothrombin time (PT)** assess the activity of vitamin K dependent clotting factor. It is quite sensitive to factor VII. Normal PT is 10-13 sec.
  - **INR** is optimally maintained at 2-3. Initially we check PT & INR daily after starting warfarin therapy. Once stable it can be checked monthly or bimonthly.

  *peak effect of warfarin is around 72-96 hr.*
Warfarin Counseling

- The patient should know that:
  - What is warfarin?
  - Why was warfarin prescribed for you?
  - Advise taking at the same time (6pm) each day.
  - If forget a dose, take it as soon as remember, as long as it is the same day.
  - Never skip a dose or take a double dose.
  - Possible Side Effects of Warfarin as bleeding.
  - Should report any symptom as Red or brown urine, red or tarry stools and Blood in vomit or mucus.
Warfarin Counseling

Using Other Medications (OTC):

- **Pain medications**
  Medications **may use**:
  Acetaminophen no more than 2000 mg per day
  Medications to **avoid**
  Ibuprofen, Naproxen, and Aspirin unless prescribed by your doctor.

- **Herbal products to avoid**
  Garlic, Ginkgo, Ginseng, Fish oil, Omega-3 fatty acids and q enzyme 10.
Diet for Warfarin Users

To help warfarin work effectively, it is important to keep **vitamin K intake as consistent as possible**

- The highest amount of vitamin K is found in green, leafy vegetables.
- Alcohol should be limited to **1 drink per day**.
- Avoid eating **mangos and liver**.
2-Heparin

- This group include:
  - Unfractionated Heparin
  - Low molecular weight heparin “LMWHs”
  - Fondaparinux “synthetic pentasaccharide”

**1-Unfractionated Heparin**

It is the standard heparin / high molecular weight heparin and it has a very high affinity for antithrombin III with significant anticoagulant activity.

**2-Low molecular weight heparin**

They have more favorable pharmacokinetics and pharmacodynamics compared to heparin. Examples; Enoxaparin, Dalteparin and Tinzaparin.
2-Heparin

Different in Pharmacokinetics between UH and LMWH:

- UH and LMWH are administered IV or SC but not orally. “polysaccharide chains are broken down by gastric acid”

*It is NOT recommended to give heparin via IM because it can cause hematoma.*

- UH has very high affinity and non-specific binding to various protein receptors, such as; those on plasma proteins, endothelial cells, platelets, **platelet factor 4 (PF4)**..... heparin-induced thrombocytopenia.

- LMWHs has lower affinity to PF4 correlates with a reduced incidence of HIT.
2-Heparin

- **Mechanism of action:**
  - UH binds to circulating Antithrombin III and potentiates its action; inhibition of thrombin (factor IIa) and factor Xa.
  - LMWHs is more selective with more targeted activity against Xa and less activity against thrombin.

  **Factor Xa: thrombin** activity is
  
  1:1 for unfractionated heparin
  
  2-4: 1 for LMWHs
2-Heparin

**Therapeutic Uses:**

1- Prophylactically to prevent postoperative thromboembolic complications in patients undergoing abdominal and orthopaedic surgeries.

2- Treatment of **acute** deep venous thrombosis and pulmonary embolism and to reduce their recurrence.

3- In **acute** phase of myocardial infarction, and post thrombolytic therapy to prevent coronary artery re-thrombosis.

4- In dialysis machines to prevent thrombosis.

5- Treating pregnant patients with prosthetic heart valves or venous thromboembolism, since they don’t cross the placenta.
2-Heparin

**Adverse effects:**

1- Bleeding is the chief complication of heparin therapy.
   - In case of haemorrhage; discontinuation of heparin and administering its antidote: Protamine sulfate is given slowly IV (1 mg/100 Units of heparin given).

2- Hypersensitivity reactions due to heparin antigenicity “due to animal source” and producing; fever, chills, urticaria or anaphylactic shock.

3- Heparin might produce abnormal liver function tests and osteoporosis (less likely to happen with LMWHs).

4- Heparin-induced thrombocytopenia (with UH).
2-Heparin

- **Laboratory Monitoring:**
  - Heparin is monitored via **activated partial thromboplastin time (aPTT)** assay which monitors factor II, X along with others.
  - Normal “non-heparinized” plasma has aPTT of 25-45 sec. This value rises to 70-140 sec in patients on heparin therapy.
  - Unfractionated heparin dose is modified according to aPTT results.
  - LMWHs have highly predictable dose-response relationships and does not require monitoring with aPTT.
  - Enoxaparin dose is based on body weight (1 mg/Kg once or twice).
  - Dalteparin and Tinzaparin dose is based on antifactor Xa units (a-Xa U) and given once daily.
3-Fondaparinux

- This is a purely synthetic administered via SC injection, once daily.
- It has predictable anticoagulant activity and does not require monitoring.
- NO significant drug interactions were reported.
- **Mechanism of action:**
  it is indirect inhibitors of Xa. Unlike heparin and LMWHs, it has no effect on thrombin.
3-Fondaparinux

- **Therapeutic Uses:**
  It is the first selective factor Xa inhibitor approved for prophylaxis against DVT in patients undergoing orthopaedic surgeries.

- **Adverse effects:**
  Bleeding mainly. It does not cause thrombocytopenia. *In fact it can be used in patients with HIT.*

- **Contraindication:**
  Patients with severe renal impairment (crcl<30 ml/minute). body weight < 50 kg.
Rivaroxaban is an orally active once daily in 10-mg doses.

The initial dose should be taken 6–10 hours after surgery, provided that haemostasis has been established.

**Mechanism of action:**
direct factor Xa inhibitor.

There is currently no specific way to reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding, unlike **warfarin**.
4-Rivaroxaban

- **Adverse effects:**
  - Bleeding (less than Warfarin).
  - Spinal/epidural hematoma.

- **Laboratory Monitoring:**
  - Periodically assess renal function as clinically indicated and adjust therapy accordingly.
Direct Thrombin Inhibitors

- **Hirudin** is a small protein isolated from the salivary glands of the medicinal leech, which has potent and specific inhibitory effects on thrombin through formation of 1:1 complex with it.
Direct Thrombin Inhibitors

- **Mechanism of action:**
  DTIs bind and inactivate free thrombin as well as thrombin-bound to fibrin
  This binding is direct and does not require antithrombin III as a cofactor for their anticoagulant activity.

- **Lepirudin and Desirudin**
  - These are recombinant hirudin derivatives. Both approved for treatment of HIT and HIT patients with thrombotic syndromes.
  - Lepirudin is administered via IV (bolus and then infusion). Desirudin is given SC twice daily
  - Lepirudin has immunologic properties, and patients might develop antihirudin Abs. Hemorrhage might occur as complication.
Direct Thrombin Inhibitors

- **Bivalirudin**
  - It has been approved for patients with unstable angina undergoing percutaneous coronary intervention (PTCA), HIT, ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.
  - It has rapid-onset, short-acting, administered via IV bolus/infusion.
  - Risk of bleeding is less than the other antithrombotics
  - No reports of antibodies formation.

- **Argatroban**
  - It has been approved for prophylaxis and treatment of HIT patients with thrombosis, during percutaneous coronary interventions in patients who have HIT or are at risk for developing it.
  - Administered SC.
Direct Thrombin Inhibitors

- **Dabigatran**
  - **Dabigatran** oral anticoagulant was developed as an alternative to **warfarin**, since it does not require maintenance of **international normalized ratio** or monitoring by frequent blood tests.
  - there is no way to reverse the anticoagulant effect of dabigatran in the event of clinically significant bleeding, unlike warfarin.
  - They have a more predictable anticoagulant response, absence of food interactions, and limited drug interactions compared with warfarin.
  - the issue of medication adherence can become problematic because The half-life periods of these agents are also shorter than that of warfarin.
  - More expensive.

- **Adverse effects:**
  Bleeding (lower than warfarin)
<table>
<thead>
<tr>
<th>drugs</th>
<th>Time of take it</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>The 15 mg and 20 mg tablets should be taken with food, while the 10 mg tablet can be taken with or without food.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Administer with or without food. take at the same time each day.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>May be taken without regard to meals.</td>
</tr>
</tbody>
</table>

*Clinical Pharmacology*
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pregnancy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Category x</td>
</tr>
<tr>
<td>Heparin</td>
<td>Category c (use LMWH is preferred)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Category B (can be used only in women can not use LMWH)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Category c.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Category c.</td>
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Thrombolytics
Thrombolytics

- Thrombolytic drugs attack and **dissolve** the formed clot to restore circulation.

- Early application of reperfusion therapy with thrombolytic agents has significantly improved the outcomes of acute MI, pulmonary embolism, DVT, stroke and other arterial thrombosis.
Thrombolytics

- **Mechanism of action:**
  - It converts plasminogen to plasmin “following the cleavage of a peptide bond” by a protease called “**tissue plasminogen activator**” that is released from the vascular endothelium.
  - **Plasmin** function to digest fibrin, however, it also digests some plasma proteins and coagulation factors.

![Diagram of the mechanism of action of thrombolytics](image)
First generation thrombolytic agents

- **Streptokinase**
  - *It is a protein purified from group C β-hemolytic streptococcus.*
  - streptokinase is considered fibrin-nonspecific drug.
  - It half life is short (30 min), infused over an hour and within 4 hours of MI.
Streptokinase

- **Streptokinase is approved for:**
  - Acute massive pulmonary embolism.
  - Acute myocardial infarction.
  - DVT (proximal).
  - Acute arterial occlusion.

- **Adverse effects:**
  1. Significant hypersensitivity reactions could occur in 3% of patients; due to prior exposure to streptococcus. Circulating antibodies will be available and the response vary.
  2. Bleeding by dissolving hemostatic plugs.
First generation thrombolytic agents

Anistreplase
- It is considered a pro-drug.
- It has a longer half life = 90 min and can be given over 3-5 hours.

Urokinase
- It is an enzyme isolated from human fetal kidney that directly degrade fibrin and fibrinogen.
- It lacks the antigenicity of streptokinase, so used in patients expected to show allergic reactions against streptokinase.
- It is much more expensive than streptokinase, half life is 15 min.
- approved for pulmonary embolism only.
Second generation thrombolytic agents

**Alteplase** (tissue plasminogen activator; tPA)
- it is fibrin-specific agent.
- It is produced via recombinant DNA technology.
- It has a short half life (5 min), so it is given via IV bolus, followed by IV infusion over 90 min.
- **Approved for acute MI, acute ischemic stroke (within 3 hours) and massive pulmonary embolism.**
Third generation thrombolytic agents

They are derived by structural modifications of the basic t-PA.

**Reteplase**
- It is highly fibrin-specific.
- It has a longer half life than alteplase (15 min), administered as 2 bolus doses 30 min apart.
- approved for STEMI.

**Tenecteplase**
- It is highly fibrin-specific.
- It has a half life is 17 min, given as single bolus.
- approved for STEMI.
Contraindications for thrombolytic therapy

1. Active internal bleeding (not including menses).
2. Previous history of intracranial hemorrhage, and ischemic stroke within 3 months.
3. Known intracranial neoplasm or vascular lesion (such as arteriovenous malformation).
4. Suspected aortic dissection.
5. Significant closed head/ facial trauma within 3 months.
Reference

- American heart association.
- Up to date.
- Lippincott pharmacology book.
Thank you