« Lec 2 »

Introduction to Antiplatelets, Thrombolytics, and Anticoagulants

- The discussion begins with **antiplatelet agents**, focusing on their mechanisms, such as inhibition of **P2Y12 receptors** and **phosphodiesterases**, explaining their role in preventing platelet aggregation.
- **Antiplatelets** are widely used and critical for daily management of thrombotic conditions.
- **Thrombolytics** act differently by breaking down **fibrin**via fibrinolysis, used in critical cases like **myocardial infarction with complete block** or severe thrombotic events. However, thrombolytics are rarely used in practice due to high risk.
- The lecture emphasizes the importance of understanding **anticoagulants**, which are more frequently used and complicated due to their narrow therapeutic indices and risks.
- The coagulation cascade is introduced:
  - **Intrinsic pathway** (contact activation, factors 12, 11, 9, 8)
  - **Extrinsic pathway** (tissue factor, factor 7)
  - Both converge on the **common pathway** involving factor 10 and thrombin (factor 2), which is pharmacologically targeted.
- Key coagulation factors relevant pharmacologically are **factor 10a** and **factor 2a (thrombin)**.

Fibrin Formation and Role of Endogenous Anticoagulants

- The **fibrinogen to fibrin conversion** is outlined as a key step in clot formation, with platelets binding fibrin to stabilize clots.
- The goal of anticoagulation therapy is to **reduce fibrin formation and dissolve clots**, essential in conditions like **unstable angina** or **venous thromboembolism**.
- Endogenous anticoagulants such as **Protein C**, **Protein S**, and **Antithrombin III** are explained as natural anticoagulants that inhibit clotting factors to maintain hemostatic balance.
- Pharmacologically, anticoagulants aim to **enhance the activity of these endogenous inhibitors** to prevent excessive clotting.
- The teacher emphasizes the **balance (homeostasis)**between coagulation and anticoagulation rather than total elimination of clotting to avoid bleeding risk.
- **Heparin** is introduced as a natural compound that dramatically enhances **antithrombin III activity** (up to 1000-fold), making it a highly effective anticoagulant.
- Heparin is not a classical drug but a biologically derived molecule, originally extracted from animal tissues.

Heparin: Chemistry, Sources, and Clinical Use

- Heparin's structure includes **pentasaccharides and glucosamine units**, essential for binding and activating antithrombin III.
- It is extracted mainly from **porcine (pig) sources** due to concerns about **bovine (cow) spongiform encephalopathy (mad cow disease)**.
- The concept of **heparin heterogeneity** is discussed: heparin extracted from different batches varies in molecular weight and activity, leading to variability in clinical effect. This **heterogeneity cannot be fully controlled** chemically, making monitoring crucial.
- Heparin's **half-life is short (~30 minutes)**, requiring intravenous or frequent subcutaneous administration, mostly in hospital settings for critically ill patients (e.g., pulmonary embolism, myocardial infarction, stroke).
- Monitoring heparin therapy uses the **Activated Partial Thromboplastin Time (aPTT)** test, aiming for a ratio of about **2-3 times the normal value** to ensure effective anticoagulation without excessive bleeding risk.
- Frequent platelet counts are mandatory due to the risk of **Heparin-Induced Thrombocytopenia (HIT)**, a serious immune-mediated complication.

- An aPTT ratio (patient aPTT/control aPTT) of 2–2.5 should be achieved throughout

Heparin-Induced Thrombocytopenia (HIT)

- HIT is an **immune reaction** where heparin binds to **platelet factor 4 (PF4)**, creating a complex recognized as foreign, triggering antibody production (hapten formation).
- These antibodies activate platelets, causing them to aggregate and release procoagulant substances like **thromboxane A2 and ADP**, paradoxically increasing clot formation despite low platelet counts.
- Two theories explain HIT:
    1. **Antibody-mediated platelet activation** leading to thrombosis and platelet consumption.
    1. **Immune destruction of platelets** causing thrombocytopenia and disseminated coagulation.
- Clinically, HIT presents as a drop in platelet count 3-5 days after heparin initiation; monitoring platelet counts during therapy is essential.
- If HIT develops, **heparin must be stopped immediately** to prevent fatal thrombosis (e.g., arterial or venous clots causing strokes or limb ischemia).

Heparin Side Effects and Low Molecular Weight Heparins (LMWH)

- Beyond HIT, heparin can cause **hyperkalemia** by reducing aldosterone secretion, requiring potassium monitoring.
- Long-term heparin use can lead to **osteoporosis** and **hair loss**, but these are rare and usually not clinically significant in short-term hospital use.
- To reduce heparin's problems (heterogeneity, monitoring, HIT risk), **Low Molecular Weight Heparins (LMWH)** were developed by chemically cleaving heparin into smaller fragments (~20 kDa).
  - LMWHs (e.g., **enoxaparin, dalteparin, tinzaparin**) have:
    - Reduced binding to PF4, lowering HIT risk
    - More predictable pharmacokinetics, reducing lab monitoring needs
    - Longer half-life allowing once or twice daily subcutaneous dosing, facilitating outpatient use
  - LMWHs primarily inhibit **factor Xa** with minimal direct thrombin inhibition, leading to loss of aPTT monitoring effectiveness.
  - LMWHs maintain anticoagulant efficacy with better safety and convenience profiles.

Transition to Oral Anticoagulants: Warfarin and New Oral Agents

- Historically, heparin was used initially, but for **long-term anticoagulation**, oral agents are preferred.
- Until 2008, **warfarin** was the only available oral anticoagulant, inexpensive but complicated in use.
- After 2008, **Direct Oral Anticoagulants (DOACs)**emerged, including:
  - **Direct thrombin inhibitors**
  - **Direct factor Xa inhibitors**
- DOACs are expensive and less accessible in low-resource settings, so warfarin remains widely used.
- Warfarin inhibits **vitamin K epoxide reductase**, blocking activation of vitamin K-dependent factors (2, 7, 9, 10) and proteins C and S (natural anticoagulants).
- The inhibition of protein C (with a shorter half-life than factor 2) initially causes a **prothrombotic state** during the first 3 days of therapy, necessitating careful management.

Warfarin Pharmacodynamics and Monitoring

- Warfarin's effect is monitored by **Prothrombin Time (PT)** and reported as **International Normalized Ratio (INR)**, targeting an INR of 2–3 for most indications.
- If INR >4, bleeding risk increases; if INR <2, clotting risk remains high.
- Vitamin K acts as the **antidote** for warfarin overdose or excessive anticoagulation.
- Warfarin's interaction with diet (e.g., vitamin K-rich foods such as tomatoes, parsley) and multiple drugs (e.g., amiodarone, fluconazole, clarithromycin) can alter its efficacy and safety.
- Genetic polymorphisms (especially in **vitamin K epoxide reductase complex subunit 1 (VKORC1)** and **CYP2C9**) affect warfarin metabolism, complicating dosing and requiring individualized therapy.

Warfarin Bridging and Clinical Management

- Due to the initial hypercoagulable state caused by protein C depletion, warfarin therapy is **bridged with heparin or LMWH** for 2-5 days until INR is therapeutic and stable.
- Once INR stabilizes, heparin is discontinued and the patient continues on warfarin alone.
- The lecture stresses the importance of **patient education and frequent monitoring** to prevent complications such as purple toe syndrome (microembolization) and bleeding.
- Home **INR monitoring devices** are increasingly used to improve patient compliance and safety.

Summary of Clinical Recommendations

- **Heparin**: Reserved for inpatient use in acute thrombotic emergencies; requires aPTT monitoring and platelet count surveillance to avoid HIT.
- **LMWH**: Preferred over unfractionated heparin for outpatient and longer-term management due to predictability and lower HIT risk.
- **Warfarin**: Main oral anticoagulant in many settings; requires INR monitoring, dietary considerations, and bridging with heparin during initiation.
- **HIT Management**: Immediate cessation of heparin and avoidance of warfarin alone in this condition; alternative anticoagulants should be used.