Platelet Factor IV-Heparin Antibodies

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Learning Objectives

- Describe the mechanism of interaction between Heparin and Platelet Factor 4
- Review the chemistry of Heparin
- Identify the consequences of antibodies to the Heparin Platelet Factor 4
- Examine the testing methodology for the anti-Platelet Factor 4 Heparin antibody
- Enhance the clinical awareness of Platelet Factor IV Antibodies
  - Population at risk
  - Clinical signs
  - Diagnosis and treatment
  - Importance of protocol
  - Medical Consequences of Poor Quality
  - Patient Satisfaction
Platelets adhere to site of vascular injury
- Neutrophil
- Red blood cell
- Platelet
- Endothelial cell
- Collagen and ECM proteins
- Smooth muscle cell
- Basement membrane

Platelet aggregation and activation
- Thromboxane A2
- ADP
- Thrombin
- Activation of coagulation cascade

Haemostatic plug formation
- Fibrin

Nature Reviews Immunology
Blood coagulation in vivo

- Platelets
  - TF (tissue factor)
  - Activated platelets

Initiation phase:
- VII
- IX
- TF-VIIa
- IXa
- Prothrombin
- Thrombin
- Stabilized, cross-linked fibrin clot

Amplification phase:
- XIa
- XI
- VIIIa
- VIII
- Va
- V
- Fibrinogen
- XIIIa
- XIII
Intrinsic system

Surface Contact

Extrinsic system

Tissue Damage

Tissue Factor

Major Site

(Xa)

Major Site

Major Site

Fibrinogen

Fibrin
Mechanism of Action

Heparin

Unfractionated heparin → Antithrombin → Factor Xa

LMWH

Low-molecular-weight heparin → Antithrombin → Factor Xa
CASE STUDY

• 57 year old female admitted with pneumonia and respiratory failure
• Admission platelet count was 230,000
• Prophylactic heparin administered
• On the 7th ICU day, the patient arrested
• Platelet count 110,000

Result
Patient expired
Diagnosis-Heparin Induced Thrombocytopenia HIT
Heparin Induced Thrombocytopenia

• Most common adverse event with heparin use is bleeding.
• Some patients develop a pro-thrombotic state known as heparin induced Thrombocytopenia (HIT)
• HIT Type I: Mild asymptomatic decrease in platelet count
• HIT Type II: Severe, potentially devastating thromboembolic complication; life and limb threatening
Heparin Induced Thrombocytopenia Type II

- An immune complex can form between heparin and platelet Factor 4 (PF4) released by platelets. This complex becomes an antigen and elicits an antibody response.
- The antibody response destroys the platelets
- Observed in 2-5% of patients treated with heparin
- The risk of thrombosis is 33-50%
dense granule containing ADP

FCγRIIa receptor

heparin binding site

free heparin

endothelial cell

heparan sulphate

α granule containing PF4

HIT-Ab

heparin-PF4 complex conformational change

HIT-Ab binds to platelets

activates endothelium

releases microparticles (tissue factor)
Clinical Signs of HIT

• Deep venous thrombosis (50%)
• Pulmonary Embolism (25%)
• Skin lesions at injection site (10-20%)
• Acute limb ischemia (5-10%)
• Warfarin associated limb gangrene (5-10%)
• Acute CVA or myocardial infarction (3-5%)
Patient Population

• Cardiopulmonary Bypass Surgery and Orthopedic Surgery are greatest risks

• HIT may also occur through:
  - Heparin flushes or subcutaneous administration
  - Heparin-coated catheters and prosthesis
  - Chronic dialysis patients
Factors Influencing the Frequency of HIT

• Type of Heparin and route of administration: Bovine UFH > Porcine UFH > LMWH Intravenous > subcutaneous

• Patient Population

• Duration of heparin therapy-use beyond day 5 increases the risk of HIT

• Sex: Female > Male
Probability of HIT

• 50% fall in platelet count
• Onset between 5 and 10 days after therapy or <1 day if heparin administered within 100 days
• New thrombosis or thrombotic signs
The Diagnosis of HIT-The four Ts

1. Thrombocytopenia
2. Timing of Platelet count
3. Thrombosis
4. Other causes of thrombocytopenia
HIT Type II-Clinico-Pathologic Diagnosis

- >50% platelet fall from Baseline or <100,000/ml.
- Onset varies-typical 5-10 days after heparin exposure; rapid < 1 day of UFH re-exposure (prior exposure within 100 days); delayed-up to 40 days after UFH exposure
- New thrombosis, skin necrosis
- No other causes
- Antibodies to complexes of HPF4
Laboratory Diagnosis of HIT

- Platelet Count
- H-PF4 antibody check
- Platelet Functional Analysis
Antigen-Base Tests

• Standardized Reagents
• Not dependent on platelet donors
• Direct testing for Anti-Platelet Factor IV antibody is available as a stat test with results in 10 minutes
Treatment of HIT

• Discontinue heparin
• Delay Warfarin until platelet count recovers
• Avoid platelet transfusion
• Treat with direct thrombin inhibitors, e.g. argatroban(Acova), bivalirudin
Conclusions

• HIT is a clinical and laboratory Diagnosis
• Patients with HIT are at risk for life and limb threatening thrombotic disease
• In critically ill patients, a negative antigen test paired with the 4T’s can exclude the presence of anti-PF4 antibodies
Elisa Vs Immuno Precipitation

• Elisa is a two step method versus a one step immuno precipitation method.
• Immuno precipitation can be performed in less than one hour.