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 anti-body
• 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
- Endothelial cell
- Platelet
- Basement membrane
- Collagen and ECM proteins
- Smooth muscle cell

Platelet aggregation and activation

- Thromboxane A2
- ADP
- Thrombin
- Activation of coagulation cascade

Haemostatic plug formation

- Fibrin

Nature Reviews | Immunology
Blood coagulation in vivo

initiation phase

TF (tissue factor) → VII → (αTHR) → TF-VIIa → (αTHR) → IX → X → Xa

amplification phase

(αTHR) → XIa → XI → (APC) → VIIIa → VIII → Va → V

prothrombin → THROMBIN

stabilised, cross-linked fibrin clot

fibrinogen → fibrin → XIIIa → XIII
Intrinsic system

Extrinsic system

Surface Contact Tissue Damage

Tissue Factor

Major Site

XII

XIIa

XIIa

Xla

IX

VII

VIIa

VIIa

VIIa

VIIa

VII

V a

II

Fibrinogen

Fibrin

Major Site

Major Site

Major Site

Xa (Thrombin)
Mechanism of Action

Heparin

LMWH
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
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%.
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.