Heparin-Induced Thrombocytopenia: Challenges in Pharmacological Management of the Co-Morbid Patient

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W.D. is a 58 yo CM admitted to the hospital for treatment of SOB later found to be a pulmonary embolism. This patient was placed on heparin and coumadin Hospital Day #1. It was noted that his platelet count steadily decreased in the following days and by Hospital Day #8 had a >50% drop. This patient was treated for Heparin-Induced Thrombocytopenia and heparin therapy was discontinued. Coumadin was also discontinued as this drug cannot be prescribed in pts with platelet counts <100. Patient was placed on lepirudin. Within 1 day of heparin discontinuation, his platelet count increased. Patient was reinstituted on coumadin and was discharged on it, though a therapeutic dose was never obtained. Patient was sent home with Arixtra, an indirect thrombin inhibitor shown to be effective in treating HIT. The case presented a challenge in dosing due to multiple comorbidities, issues with medication absorption and metabolism and drug reactions.

Background

Why you think this case is important?

Anticoagulation is a dangerous but often necessary intervention in the treatment plans of many medical conditions. It requires proper supervision and management on the part of the medical team. This case was a challenge in that the patient required therapeutic anticoagulation, yet multiple incidents occurred during the days following initiation of therapy. These events left the medical team questioning if his level of anticoagulation was adequate to prevent further thromboembolic events.

This case is important because from it I’ve learned that even though we have drugs that indicated for a therapeutic purpose, providers still encounter problems in utilizing them properly for patients. Medications and therapeutic measures must be tailored to the individual patient at all times, taking into considering body habitus, metabolism, comorbidities and individual adverse reactions.

Case Presentation

W.D. is a 58 yo Caucasian male that presented to the ED with worsening dyspnea x 2 weeks. He denied chest pain or fevers. Patient admitted having palpitations, lower extremity edema and a mild dry cough. The SOB was improved with rest and oxygen and exacerbated by exercise and the supine position. He underwent a CXR that showed a right pleural effusion with atelectasis in the right lower lobe. EKG was significant for atrial fibrillation. Patient was started on ASA, furosemide, cefotaxime, and azithromycin and admitted to a medical floor.

Hospital Day #1: W.D. is placed on heparin for DVT/PE Prophylaxis. A D-Dimer returns as 854.8. A Doppler of his lower extremities was ordered, but was non-diagnostic. Due to his obesity, the doppler could not image structures and had poor image resolution. CT shows subsegmental pulmonary embolization in the lingula, right lower lobe infiltrate and B/L pleural effusions. Patient is started on therapeutic heparin and coumadin.

Hospital Day #8: Over the past 7 days, W.D's platelets have fallen from a count of 161 on admission, now down to 80. Patient's thrombocytopenia is asymptomatic.

R.O.S. Cardiovascular- admits to palpitations. Denies CP or SOB. Extremities- significant for dryness and erythema of B/L lower extremities, B/L pedal edema, and B/L knee pain. Remaining systems were negative.
PMH: HTN, CAD, atrial fibrillation, allergic rhinitis, venous stasis dermatitis, diverticulosis
Medications: APAP, MV, ASA, metoprolol, fluticasone ns, cetirizine
PSH: appendectomy, tonsillectomy
Allergies: NKDA
Immunizations: +influenza vaccine, +pneumonia vaccine
FH: Father- DM, CAD, CA.  Mother- PE

Vital Signs: Ht 6'4'', 420 lbs, BP 142/86, P 86, R 20, T 36.4 F, PO2 96% on 2 lpm NC
Physical Exam:  Cardiac- S1 S2, irregularly irregular
Respiratory- CTAB. No rales or rhonchi
Abdomen- obese, ecchymosis
Extremities- 3+ B/L extremity edema (R>L) Right calf shows 1x2 cm open wound, dry
with crust. Positive tenderness on R. calf. B/L lower extremities are dry and
erythematous. B/L pedal edema
Neuro- AAO x 3
Remaining systems were negative

Problem list and management plan:

Pulmonary Embolism
  1. IV Anticoagulation with inpatient bridging to oral formulation
  2. Consulted Hem/Onc
  3. Laboratory studies to R/O inherited coagulopathy, hypercoagulable state,
   occult malignancy
Atrial Fibrillation
  1. Consulted cardiology
  2. IV Anticoagulation with bridging to PO
  3. Rate control while inpatient
  4. Consider outpatient rhythm cardioversion
Pleural Effusion, R/O Pneumonia
  o Empiric Antibiotic Therapy with cefotaxime and azithromycin
  o Consider thoracentesis of pleural fluid – delayed due to thrombocytopenia
Heparin-Induced Thrombocytopenia
  1. Discontinue heparin
  2. Alternative anticoagulation: lepirudin
  3. Discontinue coumadin until platelet count >100

INVESTIGATIONS

Daily BMP and CBC's were WNL except platelet count (x 10^3)
Day 1  161
Day 2  CBC not ordered
Day 3  CBC not ordered
Day 4  112
Day 5  CBC not ordered
Day 6  109
Day 7  99
Day 8  80
Day 9  76
Day 10  82
Day 11  70
Day 12  97
Day 13  108
Day 14  126
Day 15  127

Work up for Hypercoagulable state
  • Homocysteine
  • Lupus Anticoagulant
  • Anticardiolipin antibodies
- Prothrombin Gene Mutation
- Factor V Leiden
- Plasminogen Activator Inhibitor Level
- Antithrombin III (**note: cannot check ATIII levels while patient is on heparin. Heparin was d/c x 1 day. Pt administered Arixtra SQ x 1. Then restarted on heparin the following day.)

all tests - NEGATIVE.

- Protein C and S (to be evaluated in 6 months or after discontinuation of coumadin)

Work up for Heparin-Induced Thrombocytopenia type II
Heparin Induced Platelet Antibodies- NEGATIVE

DIFFERENTIAL DIAGNOSIS

Heparin Induced Thrombocytopenia – type 1
Heparin Induced Thrombocytopenia – type 2
Pseudo-thrombocytopenia
Drug-induced thrombocytopenia (Claforan, Zithromax)
Thrombotic Thrombocytopenic Purpura
Hemolytic Uremic Syndrome
Sepsis
Disseminated Intravascular Coagulation
Systemic Lupus Erythematosus
Antiphospholipid Syndrome

TREATMENT

HD #1: Heparin IV per DVT/PE prophylaxis protocol, coumadin 5mg, cefotaxime, azithromycin
HD #2 and 3: Heparin IV at PE therapeutic dose, coumadin, cefotaxime, azithromycin
HD #4 and 5: Arixtra SQ, coumadin, cefotaxime, azithromycin
HD #6: Heparin IV, coumadin, cefotaxime, azithromycin
HD #7: Same and d/c cefotaxime
HD #8-12: lepirudan, d/c heparin and coumadin
HD #13: Coumadin re-established
HD #15: Patient discharged home on Arixtra and coumadin

The treatment of HIT was initiated when the platelet count had fallen to 50% of the baseline value at admission on hospital day #8. The drug administered was lepirudan, a direct thrombin inhibitor. This drug was monitored and ordered per pharmacy dosing based on the patients aPTT.

On discharge, W.D. was sent home with an outpatient prescription coumadin and Arixtra SQ.

OUTCOME AND FOLLOW-UP

- W.D.’s hospital stay lasted 15 days.
- Discharged home on Arixtra and coumadin in addition to home medications.
- W.D.’s thrombocytopenia reached a nadir of 70.
- Following discontinuation of heparin, his platelets immediately increased at the following blood draw. This finding gives support to the diagnosis of HIT type 2, despite negative test for heparin induced platelet antibodies.
- A therapeutic INR was never achieved as an inpatient.
- W.D.’s INR was trending upwards on discharge.
- Given the strong possibility of HIT type 2, heparin should be avoided in this patient ideally. A re-evaluation of HIT antibodies can be done and if negative, some support exists for future heparin use. HIT antibodies should leave the system in ~85 days.
- In 6 weeks, patient is to follow up with cardiology to consider cardioversion of his atrial fibrillation.
In 6 months, the patient will D/C coumadin. He will then wait 2 weeks and at that time be able to check his plasma levels of proteins S and C. If one is deficient, restart anticoagulation for 12 months. If both are deficient, anticoagulate for remainder of patient’s life.

DISCUSSION

History of Heparin Use
1950’s- Clinical use as anticoagulant began
1970’s- Observation that small number of patients developed thrombocytopenia with a paradoxical, life-threatening thromboemboli
1980’s- HIT caused by IgG antibodies that activate platelets
HIT divided into 2 classes: Type 1 and 2.
MOA: Heparin binds Antithrombin III. Antithrombin III works to inhibit coagulation factors IXa, Xa, XIa and XIIa. Low Molecular Weight Heparin (LMWH) works via the same pathway but especially has an effect on Xa. Heparin is reversible with the antidote Protamine.

Pharmacological Options in Management of Anticoagulation
- Unfractioned Heparin (UFH)
- Low Molecular Weight Heparin (LMWH)’s: Lovenox (enoxaparin), Fragmin (dalteparin).
- Arixtra (fondaparinux): highly selective, indirect inhibitor of factor Xa. Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time. You cannot monitor Arixtra with pT, pTT, or Anti-Xa activity. Some studies suggest possibility of fondaparinux-induced thrombocytopenia.
- Aspirin, Plavix (clopidogrel), GIIB/IIIA antagonists, etc.

Heparin-Induced Thrombocytopenia
HIT type II is an immune complex disorder that occurs in patients following exposure to heparin. It is immune-mediated and involves the formation of antibodies against the heparin/platelet factor 4 complex (PF4). It results in thrombocytopenia, the presence of heparin-dependent antibodies (especially IgG) and an increased risk of thrombosis leading to severe morbidity and mortality.
HIT antibodies are not demonstrable in any other form of thrombocytopenia.
A second form of HIT exists but has no clinical sequela. This HIT, Heparin Induced Thrombocytopenia type I, is characterized by a lesser fall in platelet count generally within the first 2 days of therapy. This fall in platelets resolves on its own. The platelets rise even while the patient is still receiving heparin. HIT type I is non-immune mediated. This presentation will focus only on HIT type II.

Pathophysiology of HIT
The molecular interactions require a current or recent exposure to heparin. IgG antibodies recognize the heparin/PF4 complex on the platelet surface and mount an immune response. The complex and antibodies cross link on the platelet surface and activate the platelet via the Fc receptor. This triggers the platelet to release microparticles with prothrombotic activity. These particles create a positive feedback loop that activate more platelets and procoagulant microparticle release. These microparticles promote thrombin generation. Endothelial cell injury and monocyte activation from the immune response further amplify this thrombin generation. The platelet factor-4 released neutralizes the heparin that was administered. As more PF4 is released, it binds to the complexes and allows the IgG another binding spot, further enhancing platelet activation.

Why do some get HIT and others do not?
Studies have shown that tetrameric PF4 and UFH must be at an approximately 1:1 molar ratio to display optimal HIT antigenicity.
Ultra large complex of PF4 and heparin forms in HIT and is the likely antigen in HIT. At higher or lower ratios, PF4 usually forms smaller and less antigenic complexes.
Risk Factors: Who Gets HIT?

- Doses given longer than 5 days >> shorter duration of treatment
- Female > Male
- Surgical Patient > Medical Patients > Obstetric Patients
- Use of UFH (3%) > LMWH(0.5-1%) (LMWH inefficiently forms ultra-large PF4-heparin complexes)
- Bovine-derived heparin > Porcine-derived
- Adults > Pediatric patients
- Increased risk in surgical patients undergoing CABG and orthopedic procedures

Diagnosis

- Generally, patients develop thrombocytopenia 5-10 days after initiation of heparin therapy
- Early onset HIT commonly occurs if a heparin exposure occurred within the preceding months.
- Late onset HIT- HIT can be delayed and occur weeks to months following exposure.
- Platelet count falls > 50 % or falls below 100,000/mm³ platelets
- Pretest Probability- The four T's: Thrombocytopenia, timing of onset of symptoms, thrombosis (including heparin induced skin necrosis and erythematous plaques) and thrombocytopenia of other causes.

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>&gt; 50% platelet count fall to nadir ≥ 20</th>
<th>30-50% platelet count fall to nadir 10-19</th>
<th>&lt;30% platelet count fall to nadir ≤ 10</th>
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<tbody>
<tr>
<td>Timing of fall in platelet count or other sequelae</td>
<td>Onset d 5-10 or &lt; 1 d (if heparin exposure within 30 d)</td>
<td>&gt; d 10, or timing unclear, or &lt; d 1 with recent heparin 31-100 d</td>
<td>Platelet count fall &lt; d 4 (without recent heparin exposure)</td>
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<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction</td>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed</td>
<td>None</td>
</tr>
<tr>
<td>Other cause for thrombocytopenia</td>
<td>No other cause for platelet count fall is evident</td>
<td>Possible other cause is evident</td>
<td>Definite other cause is present</td>
</tr>
</tbody>
</table>

Score 0-3 : very unlikely to be HIT (<5%)
Score 4 - 5: a minority have HIT (10-30%)
Score 6 – 8: 20 to >80% have HIT, depending on the clinical setting and scorer’s experience: these patients usually require an alternative, non-heparin anticoagulant in

The are usually no bleeding manifestations from heparin-induced thrombocytopenia. The platelet fall in HIT is generally not low enough to cause petechiae, nose bleeds, or oozing from catheter sites. The nadir is usually between 50-70,000/mm³.

Diagnostic Testing
There is no gold standard in diagnostic testing. HIT requires a clinical diagnosis.

Methods of Detecting HIT Antigen
- Antigen assay (ELISA)- high sensitivity, high cost, low specificity, 10% false-negative test.
- Activation assay – donor platelets needed; not commercially available.
In patients with a high clinical risk or suspicion for HIT, heparin should be stopped and an alternative anticoagulant started BEFORE laboratory results are returned.

**So...was the patient HIT or not?**
- A positive antigen test and a progressive increase in the number of platelets over the days following discontinuation of heparin --> confirmatory for HIT.

- A negative antigen test does not rule out HIT and should be repeated after 24 hours while the patient is undergoing alternative anti-coagulant therapy. If the repeat assay is negative and platelet count does not increase, alternative diagnoses should be considered.

- If the platelet count increases but the HIT assay is negative, HIT is probable.

**Treatment**
- Immediate cessation of all heparin (SQ, IV, flushes, coated catheters)
- Initiate non-heparin anticoagulation
- Monitor for thrombosis
- Test for HIT antibodies
- Some experts recommend performing routine ultrasonography of lower extremity veins to evaluate for thrombosis.
- When the diagnosis of HIT is made, postpone overlapping treatment with PO coumadin until platelet count has reached 100,000/mm$^3$ (preferably 150.)

**Pharmacological Options in Management of HIT**

Refludan (lepirudin) is a recombinant hirudin that directly inhibits activated thrombin (platelet factor II). It is available IV and offers rapid onset. Lepirudin binds to two sites on thrombin, the catalytic site and a fibrinogen-binding site. Lepirudin prolongs the aPTT, so this test can be used to monitor effective dosing. Lepirudin is excreted in the urine, and its dosage must be adjusted in patients with renal failure. It is indicated for anticoagulation in patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications.

Danaparoid (Orgaran) is a LMW heparinoid. Due to limited bioavailability it is not available in the united states.

Argatroban- Directly inhibit thrombin. Available in IV form and has a rapid onset. It only binds to active site. Argatroban is rapidly metabolized in the liver. It affects both aPTT and PT. It is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT and indicated as an anticoagulant in patients with or at risk for HIT undergoing PCI.

Bivalirudin (Angiomax) Indicated as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) though has been shown effective by some studies in treating HIT.

Arixtra (fondaparinux) does not bind PF4 at all, suggesting that may be useful for prevention and treatment of HIT (see description above).

Coumadin (warfarin) should not be used as the sole initial treatment of HIT because of the increased risk of untoward thrombosis.

**Choosing the correct drug for your patient?**
Consider:
- Renal Function
- Hepatic Function
- Metabolism of drug via route administered

**Prevention**
- Use LMWH
• Use heparin for the shortest duration possible
• Use the smallest effective heparin dose
• Monitor platelet count on all patients receiving heparin

### Course and Prognosis
Thrombosis is the major risk from HIT. In documented HIT cases, an unrecognized thrombosis can lead to life-threatening thrombosis in ~50% of patients. This risk is not simply eliminated by discontinuation of heparin. Even if heparin is withdrawn immediately, adverse outcomes remain high. Less common manifestations include: Anaphylactoid reaction after IV heparin bolus, skin lesions at SQ heparin injection sites, and overt (decompensated) disseminated intravascular coagulation (DIC).

• Arterial thrombi: stroke, MI, mesenteric artery thrombosis, renal infarction.
• Venous thrombi: DVT, PE, adrenal infarction, cerebral dural sinus thrombosis, limb gangrene.
• Gangrenous changes in skin can occur at sites of heparin injection.
• Thrombosis 30-50%
• Amputation 20%
• Death 30%

Intervention with the direct thrombin inhibitors decrease the length of time with thrombocytopenia and decrease the risk of developing thrombosis. The trade off is an increased incidence of significant bleeding.

### Was W.D. HIT? 4 T’s, Antigen testing, and Response to treatment.

- Thrombocytopenia- platelets dropped to 70,000/mm$^3$. A 56% decrease in platelets from admission.
- Onset of Platelet drop- Hospital Day #?? It is unknown if the onset was within the first two days of treatment, as platelets were not assessed on days 2, 3, and 5. Though, the count was decreased on day 4. He could have had type I HIT with a slow drop in platelets. Though, HIT type II is a greater concern given his already hypercoagulable state. Even though his platelet drop occurred early, the benefit outweighed the risk in assuming he had a type II reaction. If W.D. had been exposed to heparin in the preceding months, the chance of a early drop in HIT type II is greater.
- Thrombosis- none of significance noted. Positive for ecchymosis on abdomen.
- Other causes of thrombocytopenia- drug-induced thrombocytopenia a real possibility in that initiation of heparin occurred on the same day as initiation of cefotaxime, a rare cause of thrombocytopenia.
- Heparin-induced antibody test was negative.
- W.D. responded immediately to discontinuation of heparin. His platelet count on the day following increased.

### Did W.H. Receive the appropriate treatment?

W.D.’s hypercoagulable state?
Is W.D. HIT?
Was treatment with SQ Arixtra appropriate?
Is W.D. properly anticoagulated?

The patient in this case suffered a pulmonary embolism and subsequently needed therapeutic measures to ensure his safety from another thromboembolic event. Among those in whom the PE is diagnosed, 2 percent die within the first day and 10 percent have recurrent pulmonary embolism; the death rate among the latter group is 45 percent. The important issue raised during his treatment was the etiology of the pulmonary embolism. Was it due to atrial fibrillation or was there another cause of his hypercoagulable state? Also, if that state still existed during hospital treatment of the PE, was he properly anticoagulated?

Instituting heparin as the anticoagulant of this patient was a reasonable decision. When thrombocytopenia was first observed in the laboratory reports, HIT was part of the differential immediately, though it was not diagnostic at that point. A decision towards...
watchful waiting was made and proved to be key as the diagnosis was supported with a further fall in following days. Medical providers must be aware of drug side effects. Heparin-Induced thrombocytopenia is a well known complication of heparin therapy and thus should not be missed by the observant health care provider.

A number of drugs are available to anticoagulate a patient via various interactions in the coagulation cascade. In the case of W.D., he was not able to receive heparin due to HIT, and because his platelets dropped below 100 could not receive coumadin. W.D. was discharged to home on SQ doses of Arixtra. It was brought to the attention of the medical team by the clinical pharmacologist that in a man of his size, there is no certainty of absorption of this newer and less studied SQ medication. His large weight and fat distribution suggests an erratic absorption and metabolism of the drug. There are no laboratory values to follow in Arixtra therapy. On discharge the patient was on coumadin, but the INR had not yet become therapeutic. Did we discharge this patient home sub-therapeutic on both anticoagulant therapies and how are we to know?

The solution would have been to keep the patient until his INR was therapeutic, at the minimum. The medical staff was pressured by a frustrated and bored patient that was threatening to leave the hospital against medical advise. Instead, he was discharged by the medical staff but sub-therapeutic and with medications via a SQ route of questionable efficacy. The better medical decision may have been to keep the patient as long as necessary as the risk was too great in this patient for him to go home.

**Literature Search:**


For obese patients, dose capping of low molecular weight heparin is not warranted, and twice-daily enoxaparin is preferred over once-daily dosing. Anti-Xa monitoring is perhaps not necessary for patients weighing less than 190 kg (418 lb). If the patient weighs more than 190 kg and anti-factor Xa monitoring is available, LMWH therapy may be based on actual body weight with dose adjustments based on anti-factor Xa levels. If anti-factor Xa monitoring is not available for patients weighing more than 190 kg, LMWH therapy should be dosed according to actual body weight. Obese patients receiving fondaparinux cannot have their therapy monitored by anti-factor Xa levels. **It is unknown what weight should generate concern about the use of fondaparinux.**


Once-daily subcutaneous fondaparinux was at least as effective (not inferior) and safe as twice-daily, body weight–adjusted enoxaparin in the initial treatment of patients with symptomatic deep venous thrombosis.


The immune response to heparin appears to be transient. PF4–heparin antibodies disappear from the circulation within a median of 85 days. Although there are reports of limited repeated exposure to heparin in patients in whom the antibodies cleared, concern remains regarding repeated exposure to heparin in those who have had heparin-induced thrombocytopenia. Although rigorous data are lacking, patients should receive alternative anticoagulant agents for most indications.

**LEARNING POINTS/TAKE HOME MESSAGES - 3 to 5 bullet points**

1. Heparin-Induced Thrombocytopenia, type II, can occur 5-10 days after initiation of any form of heparin therapy and increases a patients risk of thrombosis related morbidity and mortality.

2. In HIT, platelet count falls > 50 % or falls below 100,000/mm³ platelets.
Consider HIT in patients receiving any form of heparin and order appropriate laboratory studies to monitor patient following drug administration and diagnosis.

Consider using LMWH or Arixtra in place of UFH in thromboembolic prophylaxis and treatment.

Use all drugs only when clinically necessary and for the shortest duration possible to safely treat the patient.

Consider inappropriate absorption of subcutaneously injected drugs in the morbidly obese patient.

REFERENCES


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