Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

Presented as a Midday Symposium at the 44th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 7, 2009
Las Vegas, Nevada
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Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

AGENDA

11:30 a.m. – 11:50 a.m. Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines
   Edith Nutescu, Pharm.D., FCCP

11:50 a.m. – 12:25 p.m. Review of Current and Emerging Therapies for Heparin-Induced Thrombocytopenia
   Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)

12:25 p.m. – 12:55 p.m. Practical Management of Patients with Heparin-Induced Thrombocytopenia
   Maureen Ann Smythe, Pharm.D.

12:55 p.m. – 1:15 p.m. Heparin-Induced Thrombocytopenia (HIT) Clinical Pearls
   Faculty

1:15 p.m. – 1:30 p.m. Panel Discussion and Questions and Answers
   Faculty

FACULTY

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Director, Antithrombosis Center
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The faculty and planners report the following relationships:

**Edith Nutescu, Pharm.D., FCCP, Chair**

Dr. Nutescu declares that she has no relationships pertinent to this activity.

**Maureen Ann Smythe, Pharm.D.**

Dr. Smythe declares that she is on the GlaxoSmithKline speaker's bureau.

**Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)**

Dr. Spinler declares that she is on the GlaxoSmithKline speaker’s bureau and consults for Baxter.

**Erika Thomas, M.B.A., B.S.Pharm.**

Ms. Thomas declares that she has no relationships pertinent to this activity.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

ACTIVITY OVERVIEW

Annually, millions of patients receive heparin for indications from routine catheter flushes to preventing the formation of thrombi during cardiac bypass surgery. Although heparin is an extremely effective anticoagulant, like any drug, it is not without adverse effects. Heparin-induced thrombocytopenia (HIT) is an immune-mediated response to heparin.

Faculty in this interactive symposium will provide attendees with an overview of HIT, including current treatment guidelines. Emphasis will be placed on the challenges associated with currently available treatments and highlight emerging therapeutic options, including both drugs currently undergoing clinical trials and novel use of currently available antithrombotics. The recently updated clinical guidelines for the treatment and prevention of HIT, published by the American College of Chest Physicians, will be highlighted. This symposium will also feature clinical pearls showcasing where pharmacists can have the greatest impact in the treatment of patients with HIT.

ACTIVITY OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

- Define the criteria for diagnosis of heparin-induced thrombocytopenia (HIT).
- Summarize the current guidelines for the monitoring and treatment of HIT.
- Describe the most common challenges associated with currently available treatments for HIT.
- Name at least two emerging therapeutic options for the treatment of HIT.
- Identify three opportunities for pharmacist intervention to improve the care of patients with HIT.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 2.0 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity #204-000-09-432-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP Learning Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the five-digit session code announced during the activity.

Available soon at http://ashpmedia.org/symposia/HIT

So that this educational activity can be shared with a wider audience, a Web-based version of it is being developed. Encourage your pharmacist colleagues who were unable to attend the Midyear to look for this free online continuing pharmacy education activity beginning in March 2010.

Please note that individuals who claim CPE credit for the live symposium are ineligible to claim credit for the Web-based activity.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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6. Click submit to receive the attestation page.

7. Confirm your participation and click submit. Your transcript page will appear.

8. Click on view/print statement of credit next to the meeting name to print your CPE statement.

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Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

Edith Nutescu, Pharm.D., FCCP, Chair
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Edith A. Nutescu, Pharm.D., FCCP, is Clinical Professor in the Department of Pharmacy Practice and Center for Pharmacoeconomic Research at the University of Illinois at Chicago College of Pharmacy. She also serves as Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center. As a clinician and educator, Dr. Nutescu has contributed extensively to the care of patients and the education of students and health care providers on topics related to cardiovascular therapeutics.

Dr. Nutescu maintains an active clinical practice and research program. Her research and practice interests are in the areas of comparative effectiveness, health services and outcomes, with emphasis in cardiovascular diseases, stroke, thrombosis, and antithrombotic therapies. Dr. Nutescu has authored or co-authored over 100 scientific articles, book chapters, and abstracts published in the science and medical literature and has served as a reviewer for the literature in her field. She serves on the Editorial Boards for the American Journal of Health-System Pharmacy (AJHP) and Annals of Pharmacotherapy. She has lectured extensively both nationally and internationally on topics related to hyperlipidemia, thrombosis, stroke, and cardiovascular diseases. Dr. Nutescu serves as the Vice-President and on the Board of Directors of the Anticoagulation Forum, and has served on the National Consumers League Senior Outpatient Medication Safety Coalition - Oral Anticoagulant National Advisory Board. Dr. Nutescu was the only pharmacist member nominated to serve on the Steering Committee for the National Quality Forum and the Joint Commission on the Accreditation of Healthcare Organizations - National Consensus Standards for the Prevention and Care of Venous Thrombosis. She has been recognized as a Fellow of the American College of Clinical Pharmacy and is the 2009 recipient of the American College of Clinical Pharmacy’s Clinical Practice Award.

Dr. Nutescu earned her Doctor of Pharmacy with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, Dr. Nutescu went on to complete an American Society of Health-System Pharmacists–accredited Pharmacy Practice Residency at Lutheran General Hospital—Advocate Health Care and a Primary Care Specialty Residency at the University of Illinois at Chicago Medical Center.
Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines

OVERVIEW

Heparin-induced thrombocytopenia (HIT) is an uncommon but extremely serious adverse effect associated with heparin use. The immune-mediated platelet activation and thrombin generation seen during HIT can lead to severe and unusual thrombotic complications. Morbidity and mortality associated with HIT is disturbingly high—up to 50% of patients who develop the disorder will suffer a thrombotic complication or die within 30 days in the absence of treatment. The diagnosis of HIT is based on laboratory findings that confirm heparin antibody formation and platelet activation. Platelet counts typically begin to fall 5 to 10 days following initiation of heparin and reach a nadir by days 7 to 14. The development of thrombocytopenia can be delayed (delayed-onset HIT) up to 30 days, and begin several days after heparin has been stopped in patients naive to heparin therapy. Conversely, so-called rapid-onset HIT can occur rapidly and abruptly (within 24 hours following heparin initiation) in patients with a recent exposure to heparin (i.e., previous 3 months).

Platelet counts commonly fall below 150,000 mm\(^3\) but rarely nadir as low as 20,000 mm\(^3\). In some cases, overt thrombocytopenia may not occur, but a drop in platelet count greater than 50% from baseline is considered indicative of HIT. The frequency of immune-mediated HIT is most powerfully related to the duration and type of heparin used and to a lesser extent the dose and route of administration. The estimated overall incidence of HIT after 5 days of UFH use is 1% to 3% but the cumulative incidence may be as high as 6% after 14 days of continuous intravenous use. The incidence of HIT with low dose subcutaneous UFH in medical patients has been reported to be approximately 1%. Low-molecular-weight heparins are associated with a significantly lower risk of HIT (<1%). The incidence of HIT is higher with bovine UFH versus porcine UFH. In addition, the HIT risk varies with the exposed patient population: surgical patients > medical patients > pregnant patients. The relatively high frequency of thrombotic complications and poor outcomes associated with HIT emphasize the need for prompt recognition and diagnosis. The diagnosis of immune-mediated HIT is made based on clinical findings supplemented by laboratory tests confirming the presence of antibodies to heparin or platelet activation induced by heparin.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review the epidemiology and incidence of heparin-induced thrombocytopenia (HIT).
- Discuss approaches for laboratory and clinical diagnosis of HIT.
- Formulate an appropriate treatment plan for a patient who develops HIT consistent with clinical practice guidelines.
Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines

Edith Nutescu, Pharm.D., FCCP
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Learning Objectives

• Review the epidemiology and incidence of heparin-induced thrombocytopenia (HIT)
• Discuss approaches for laboratory and clinical diagnosis of HIT.
• Formulate an appropriate treatment plan for a patient who develops HIT consistent with clinical practice guidelines.

Heparin-Induced Thrombocytopenia

• Serious immune-mediated prothrombotic disease induced by heparin
• Defined by a falling platelet count during or following heparin treatment, with or without thrombotic complications
• Paradoxical hypercoagulable state that can potentially lead to new thromboses, amputation, and death
• Patients receiving any type of heparin at any dose by any route of administration may be at risk of developing HIT, making it difficult to diagnose

Incidence

- More than 12 million patients are exposed to heparin each year in the United States.
- Estimated that 600,000 new cases of HIT occur each year. Of these, as many as:
  - 300,000 patients develop thrombotic complications
  - 90,000 patients die
- HIT occurs in
  - 1%-5% of patients receiving unfractionated heparin (UFH)
  - 0.2%-0.8% of patients treated with LMWH

Frequency of HIT

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Adults (UFH postoperatively)</td>
<td>1.0% to 2.4%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cardiac transplant</td>
<td>11%</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td></td>
</tr>
<tr>
<td>UFH postoperatively</td>
<td>4.8%</td>
</tr>
<tr>
<td>LMWH postoperatively</td>
<td>0.6%</td>
</tr>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.3%</td>
</tr>
<tr>
<td>Critical care</td>
<td>0.4%</td>
</tr>
<tr>
<td>Those treated with subcutaneous,UFH</td>
<td>0.8%</td>
</tr>
<tr>
<td>Newly treated with hemodialysis</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

The Risk of HIT

- Bovine > porcine heparin
- Surgical patients > than medical
- Female > male
- Recent heparin exposure – rapid onset HIT
- Minimized by use of LMWH over heparin in surgical patients
- Contaminated heparin?
Heparin Contamination

• Jan 2007 – April 13th 2008: 131 reports to FDA of deaths of patients receiving heparin

• 1st 75 days of 2008: 123 deaths with 78 having one or more allergic / hypotensive symptoms

• Heparin contaminant: oversulfated chondroitin sulfate (OSCS), can activate contact system to generate bradykinin

Contaminated Heparin and HIT

<table>
<thead>
<tr>
<th>Country</th>
<th>OSCS-heparin Distributed</th>
<th>Period Before Contamination (n)</th>
<th>Period After Contamination (n)</th>
<th>% Increase in Positive Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>No</td>
<td>45 / 373</td>
<td>51 / 409</td>
<td>13.3</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>32 / 459</td>
<td>64 / 405</td>
<td>100</td>
</tr>
</tbody>
</table>

Positive tests include IgG EIA and functional assay


Diagnosis of HIT

• Timing of thrombocytopenia
• Degree of thrombocytopenia
• Associated clinical syndromes
• Thrombosis
• Response to therapy
• Supportive laboratory studies
Differential Diagnosis of HIT

- Hemodilution post-surgery
- Sepsis
- DIC (multiple causes besides HIT)
- Cancer-associated DIC
- Antiphospholipid syndrome
- Thrombolytic therapy
- EDTA-induced pseudothrombocytopenia
- GP IIb/IIIa inhibitor-induced thrombocytopenia
- Drug-induced thrombocytopenia (other than heparin)
- Post-transfusion purpura
- Thrombotic thrombocytopenic purpura
- Non-immune heparin-associated thrombocytopenia


Diagnosis of HIT

- Seroconversion without TCY is not HIT
- Diagnosis of HIT is made when HIT antibody is present along with:
  - otherwise unexplained fall in platelet count of ≥ 50%
  - skin lesions at heparin injection sites
  - acute systemic reactions
  - +/- thrombotic complications

TCY = thrombocytopenia

Warkentin TE Chest 2008

HIT: Unusual Presentation

- Heparin-induced skin lesions at injection sites
- Acute anaphylactoid reactions
- Warfarin associated venous limb gangrene
- Classic warfarin-induced central skin necrosis
- Adrenal hemorrhagic infarct

Thromboembolic Complications

A typical HIT case will occur at (on average)

A. 1-2 days post-heparin exposure.
B. 9 days post-heparin exposure.
C. More than 10 days post-heparin exposure.
D. No mean time has been determined.

Clinical Presentation

Typical Presentation:
- Thrombocytopenia typically develops 5-14 days following initiation of heparin.
  Platelet count reduction may be:
  - At least a 50% drop from pre-heparin level
  - ≤ 150 x 10⁹/L
  - Very low platelet counts are rare

Less Common Presentations:
- Rapid-onset
  - Occurs within minutes to hours of re-exposure to heparin or LMWH
- Delayed-onset
  - Occurs up to several weeks after heparin cessation and often after hospital discharge

Temporal Patterns of Thrombocytopenia in HIT

- Rapid-onset HIT (hours-days)
- Typical HIT Mean day 9 (4-14 days)
- Delayed HIT (9-40 days)

Insights into Clinical Presentation

- 20% of patients have platelet count nadir > 100 x 10^9/L
- In ICU Patients thrombosis is a better clinical indicator of HIT than thrombocytopenia; if not evident look
- Thrombosis may precede thrombocytopenia
- Thrombotic risk correlates with the magnitude of the platelet count decrease
- Consider delayed onset HIT: thrombosis + thrombocytopenia 5-30 days after heparin stopped

Onset of Platelet Count Decrease and TEC

% of patients with Platelet count decrease before TEC
% of patients with Platelet count decrease after TEC

Day of TEC = day 0

Pathophysiology
How does an anticoagulant cause life threatening clotting?

Depiction on Heparin-induced Epitopes on PF4

Adapted from Darvoren A, Aster RH. Am J Hematol. 2006;81:36-44.

Pathophysiology of HIT

Laboratory Assays to Confirm HIT Following Initiation of Therapy

<table>
<thead>
<tr>
<th>Assay</th>
<th>Component measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin-release assay (SRA)1-3</td>
<td>14C-serotonin released from platelets</td>
<td>Highly sensitive and specific</td>
<td>Costly, time-consuming, and technically demanding (involves radioisotopes)</td>
</tr>
<tr>
<td>Heparin-induced platelet aggregation assay (HIPA)1-3</td>
<td>Platelet aggregation</td>
<td>Highly specific, easy</td>
<td>Low sensitivity and technique-dependent</td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay (ELISA)1-3</td>
<td>Presence of heparin-dependent antibodies</td>
<td>Highly sensitive, easy, rapid turnaround time</td>
<td>Low specificity (false positives)</td>
</tr>
<tr>
<td>PIFA® Heparin/PF4 Rapid Assay4</td>
<td>Presence of PF4 antibodies</td>
<td>Highly sensitive and specific</td>
<td>Fairly new with limited clinical history, positive and negative controls not provided</td>
</tr>
</tbody>
</table>


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Which of the following statements is true?

A. Discontinuation of heparin eliminates risk for HIT.
B. Platelet transfusions are contraindicated in HIT.
C. Arterial and venous HIT occur at about the same rate.
D. All of the above.

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The Burden of HIT

- Risk of new thrombosis ~ 30%-75% in HIT patients ... despite d/c of heparin
- Platelet transfusions are contraindicated; 4/5 HIT patients died after platelet transfusion
- Venous 4× more frequent than arterial
  - DVT (50%)
  - PE (25%)
  - Cerebral vein; adrenal hemorrhagic infarction
- Arterial
  - Aortic (10%)
  - Myocardial infarction (3%-5%)
  - Miscellaneous arteries...renal, mesenteric, spinal (rare)
- Amputation: 10% risk
- Death: 20%-30%
- Financial impact
  - HIT cases had incremental cost ↑ of $41,133/case

Objectives of Treatment for HIT

Why
• Minimize complications of HIT, including thrombosis, morbidity, and mortality

How
• Interrupt the immune response
  – Immediately discontinue heparin use
  AND
• Inhibit effects of thrombin
  – Stabilize hypercoagulable state
  – Treat active thrombosis
  – Prevent new thrombosis

Mana
g
ment of Suspected or Confirmed HIT
The 6 “A’s”

• Avoid and discontinue all heparin; including LMWH
• Administer non-heparin anticoagulant
• Anti-PF4/heparin antibody test for confirmation
• Avoid platelet transfusions
• Await platelet count recovery before initiation of warfarin
• Assess for lower extremity thrombosis

HIT Management

- Initiate alternative non-heparin anticoagulant for strongly suspected or confirmed HIT whether or not complicated by thrombosis
  - Danaparoid 1B
  - Lepirudin 1C
  - Argatroban 1C
  - Fondaparinux 2C
  - Bivalirudin 2C

Chest 2008; 133: 340-380s.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

SELECTED REFERENCES AND RESOURCES

7. PIFA® Heparin/Platelet Factor 4 Rapid Assay [package insert]; 2005.
SELF-ASSESSMENT QUESTIONS

1. Patients receiving any type of heparin at any dose by any route of administration may be at risk of developing HIT
   a. True
   b. False

2. A typical HIT case will occur at (on average):
   a. 2-3 days post heparin exposure
   b. 9 days post heparin exposure
   c. More than 10 days post heparin exposure
   d. No mean time has been determined

3. Rapid-onset HIT occurs within minutes to hours of re-exposure to heparin or LMWH.
   a. True
   b. False

4. The ELISA assay is more sensitive and more specific than the serotonin release assay used to confirm the diagnosis of HIT.
   a. True
   b. False

Answers
1. a
2. b
3. a
4. b
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology) is Professor of Clinical Pharmacy in the Department of Pharmacy Practice and Pharmacy Administration at the Philadelphia College of Pharmacy, University of the Sciences in Philadelphia. She is also an adjunct faculty member in the Cardiovascular Division in the Department of Medicine at the University of Pennsylvania. Dr. Spinler serves as a preceptor to pharmacy students and performs clinical research at the Hospital of the University of Pennsylvania, coronary intensive care unit.

Dr. Spinler has authored more than 150 research articles, reviews, and books chapters and given more than 300 continuing education programs in the area of acute coronary syndrome, antiplatelets and anticoagulants. In 2004, she was awarded the American Society of Health-System Pharmacist Award for Sustained Contributions to the Literature of Pharmacy Practice. She currently serves on the editorial boards of several biomedical journals including *Annals of Pharmacotherapy, Pharmacotherapy, American Journal of Managed Care*, and *Drugs*. Dr. Spinler chaired the 2005-2010 Council of Experts, United States Pharmacopeia, Cardiovascular Expert Committee and served on USP’s Medicare Model Guidelines Committee. She was a member of the Steering Committee for the CRUSADE Registry and is currently a member of the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR®) Practice Innovation and Clinical Excellence (PINNACLE Registry™) Steering Committee, serves on the Executive Team of the ACC/Institute for Health Care Improvement (IH) Hospital to Home (H2H) National Quality Improvement, the Steering Committee of the Interdisciplinary Working Group of the American Heart Association (AHA) Quality of Care and Outcomes Research (QCOR) Interdisciplinary. In 2009 she was appointed to the National Quality Forum Consensus Standards for Patient Outcomes Cardiology Technical Advisory Panel.

Dr. Spinler received her Bachelor of Science and Doctor of Pharmacy degrees from the University of Minnesota in Minneapolis. She completed a pharmacy residency and research fellowship in cardiovascular critical care pharmacy at the University of Illinois at Chicago. Dr. Spinler is a Board Certified Pharmacotherapy Specialist with Added Qualifications in Cardiology. She is a Fellow of the American College of Clinical Pharmacy (ACCP) and was awarded Fellow of AHA Cardiovascular Clinical Council and inaugural QCOR Fellow in 2009.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)

PRESENTATION

Review of Current and Emerging Therapies for Heparin-Induced Thrombocytopenia

OVERVIEW

The 2008 American College of Chest Physicians heparin-induced thrombocytopenia (HIT) guidelines recommend lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], or bivalirudin [Grade 2C]) over the further use of unfractionated heparin or low-molecular-weight heparin for patients with strongly suspected (or confirmed) HIT, with or without thrombosis. Argatroban and lepirudin are direct thrombin inhibitors (DTIs) that carry FDA-approved labeled treatment indications for HIT with/without thrombosis. American College of Chest Physician 200 guideline-recommended dosing for argatroban and lepirudin, as well as target activated partial thromboplastin time (aPTT) for lepirudin are lower than those recommended in the product labeling.

Clinical considerations when using argatroban include the need for dosing adjustment downward for initial infusions for patients with hepatic dysfunction, heart failure, multiple organ system failure, severe anasarca, and for patients in the early post-cardiac surgery period secondary to reduced clearance. There is one published nomogram for dosing adjustments of argatroban based upon achieving a target aPTT. Lepirudin is renally eliminated and should not be administered to patients with acute renal failure or those receiving dialysis. Lepirudin administration is associated with the development of antihirudin antibodies. Readministration of lepirudin has been associated with anaphylaxis and the ACCP guidelines recommend selection of an alternative nonhirudin anticoagulant for those patients.

When transitioning between an injectable anticoagulant and warfarin, direct thrombin inhibitors (argatroban > bivalirudin > lepirudin) increase the INR and make the transition to stable oral anticoagulation difficult. Clinicians may incorrectly interpret the elevation and stop the DTI prematurely putting the patient at risk of thrombosis. They may incorrectly administer vitamin K thereby increasing the length of time to achieve the target INR with warfarin. Fondaparinux offers the advantage of subcutaneous administration, lower costs than DTI, and no effect on the INR but has a long half-life and no specific antidote making reversal difficult. Fondaparinux is contraindicated in patients with creatinine clearance of less than 30 mL/min. When administering fondaparinux in patients with acute HIT, weight-based “treatment” doses, identical to those given for treatment of acute venous thromboembolism are recommended rather than a “prophylaxis” dose. Bivalirudin offers the advantage of significant experience in the setting of percutaneous coronary intervention and cardiopulmonary bypass for cardiac surgery. It is also the lowest cost DTI. Data using with fondaparinux and bivalirudin are limited to case series and small observational studies.

Desirudin is a subcutaneously administered DTI previously approved in the U.S. for venous thromboembolism prophylaxis in patients undergoing hip replacement. It is currently being compared to argatroban in a clinical trial of patients with suspected HIT. There are advantages and disadvantages to each currently recommended treatment for HIT. Clinicians should use patient-specific information to select the best therapy.
LEARNING OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

• List advantages and disadvantages of argatroban, lepirudin, fondaparinux and bivalirudin for treatment of heparin-induced thrombocytopenia (HIT).

• Given a patient case, select initial dosing of argatroban.
Current and Emerging Therapies for HIT

Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)
Professor of Clinical Pharmacy
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University of the Sciences in Philadelphia
Philadelphia, Pennsylvania

Learning Objectives

- List advantages and disadvantages of argatroban, lepirudin, fondaparinux and bivalirudin for treatment of HIT.
- Given a patient case, select initial dosing of argatroban.

Argatroban Clinical Considerations

- FDA approved for HIT/HITTs and PCI in setting of HIT/HITTS
- More patients treated with bivalirudin for PCI than argatroban
- Hepatic clearance requiring dose adjustment for patients with hepatic disease
- 2008 ACCP Chest Guideline dosing lower than product labeled dose
- Reports of reduced clearance and increased effect in fluid-overloaded patients
- Lacks data in patients undergoing CPB during cardiac surgery
- Increases INR so makes transition to warfarin difficult
  - Greater INR effect than lepirudin

Argatroban Dosing

- **Product Label**
  - 2 mcg/kg/min (or 0.5 mcg/kg/min if hepatic impairment)
  - No initial bolus
  - Adjusted to achieve aPTTs 1.5-3 times the baseline value

- **2008 ACCP Chest Guidelines**
  - Initial infusion rate, 2 mcg/kg/min IV
  - No initial bolus
  - Reduced initial infusion rate (0.5–1.2 mcg/kg/min) is appropriate in certain patient populations
    - Heart failure
    - Multiple organ system failure
    - Severe anasarca
    - During the early post-cardiac surgery period
  - Target aPTT not specified

Lepirudin

- **Derived from the saliva of the medicinal leech Hirudo medicinalis**
  - Shares 63 of 65 amino acids
- **Renally eliminated**
  - Dosing adjustment required if CrCl ≤ 60 mL/min
  - Avoid in acute renal failure and dialysis
- **Increases INR making warfarin transition difficult**
  - Less than argatroban and bivalirudin
- **Anaphylaxis/anaphylactoid reactions estimated to occur in 0.015%**
  - Increased risk with readministration (0.16%)
  - If readministering, consider ICU/ICU Step-down setting
  - Administer non-hirudin anticoagulant
- **2008 ACCP Chest Guideline dosing and aPTT target lower than product labeled dose**

Lepirudin Dosing

- **Product label**
  - Bolus dose: 0.4 mg/kg IVP (over 15-20 seconds) (maximum initial bolus dose: 44 mg)
  - Continuous infusion at 0.15 mg/kg/hour (maximum initial infusion dose: 16.5 mg/hour)
  - aPTT target is 1.5-2.5 x the median of the aPTT normal range

- **2008 ACCP Chest Guidelines**
  - Administer bolus only in life-threatening situations
  - Bolus 0.2–0.4 mg/kg IV
  - Maximum initial infusion rate 0.10 mg/kg/h IV
  - aPTT target is 1.5–2.0 x patient’s baseline or mean of laboratory normal range
Emerging Treatments

• Fondaparinux

• Bivalirudin

Fondaparinux

• Advantages
  – Does not cause HIT
    • While heparin anti-PF4 antibodies have been observed during administration of fondaparinux
      – They do not bind well to PF4 in vitro in the presence of fondaparinux, even though they recognize well the epitopes on PF4 in the presence of UFH or LMWH.
      – Platelet count recovery in patients observed during administration of fondaparinux in patients with HIT
      – One case of fonda-associated thrombocytopenia could have been delayed HIT from heparin administration
  – Avoids elevated INR seen with DTIs
  – Facilitates transition to warfarin
    • More "consistent" anticoagulant treatment during warfarin transition


Fondaparinux

• Advantages
  – Acquisition cost less expensive than DTIs
  – Easier transition to warfarin
  – No effect on INR
  – Can be administered in the outpatient setting
  – Listed as a 2C recommendation in the 2008 ACCP guidelines
    • For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], bivalirudin [Grade 2C]) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA (Grade 1B).

Fondaparinux

• Disadvantages
  – Does not inhibit circulating thrombin
    • Indirect-acting Factor Xa inhibitor prevents production of thrombin
  – No antidote and long half-life
    • DTIs have shorter half lives
    • May be reversed with recombinant factor VIIa
  – Contraindicated if CrCl < 30 mL/min
  – Published data supporting its use are weak
    • Most are case reports, uncontrolled case series
    • < 100 patients total
    • Limited information on fondaparinux dosing in some reports


“Best” Data: Lobo et al.

• Eligible patients
  – Otherwise unexplained > 50% fall in platelet count with recent (within 2 weeks) exposure to heparin
    – + heparin PF4 Ab test or + SRA
  • Excluded patients with CrCl < 30 mL/min
  • Excluded patients at high bleeding risk


“Best” Data – Lobo et al.

• Historical control group identified from list of patients with + heparin PF4 Ab test from 4/03 to 10/05 and chart review performed.
  – N=10 (6 with arterial and/or venous thrombosis)
  – DTI treatment with either lepirudin or argatroban according to a standard hospital protocol required
• Fondaparinux
  – N=7
  – Subjects without thrombosis (N=1)
    • 2.5 mg subcut once daily
  – Subjects with arterial and/or venous thrombosis (N=6)
    • 5 mg subcut once daily in patients weighing ≤ 50 kg
    • 7.5 mg subcut once daily in patients weighing 50-100 kg
    • 10 mg subcut once daily in patients weighing > 100 kg

Study Outcomes – Lobo et al.

- Platelet count recovery
  - 7/7 fondaparinux patients versus 8/10 historical controls

- Patient Deaths
  - 2 in historical control group versus 0 in fondaparinux group

- New thromboembolic events
  - No new thromboembolic events in fondaparinux group
  - No new thromboembolic events in historical control group while being treated with DTI


Study Outcomes – Lobo et al.

- Limb amputation
  - 1 in the fondaparinux group after unsuccessful thrombectomy
  - 1 in historical control group associated with venous limb gangrene

- Venous limb gangrene
  - 0 in the fondaparinux group
  - 4/10 in the DTI group all associated with warfarin initiation prior to or on same day as DTI

- Bleeding complications
  - (≥ 2 g/dL Hg drop)
    - 3/7 in fondaparinux group: occurred off treatment
    - 5/10 in historical control group occurring during DTI treatment
  - Transfusion
    - 4/7 in fondaparinux group
    - 4/10 in historical control group


“Best” Data – Grouzi et al.

- Retrospective study
- Chart review Jan 2003 and Jan 2008
- Eligible Patients
  - 50% platelet count fall
  - + PF4 ELISA and + particle gel immunoassay
- 24 patients with HIT treated with fondaparinux
  - 5 mg < 50 kg, 7.5 mg 50-100 kg, 10 mg > 100 kg
- 20 patients in control group treated with lepirudin
  - 0.15 mg/kg/hr (no bolus) adjusted to aPTT 2-3 x control
- No patients with renal dysfunction included
- IVIG given to about 20% of patients
- Oral anticoagulation initiated in all patients when platelet count > 150 x 10^9/L
  - Fondaparinux discontinued when INR > 2 for 2 consecutive days
  - Overlap procedure with lepirudin not described

Study Outcomes – Grouzi et al.

• Platelet count recovery
  – All study patients

• Patient deaths
  – 1/24 fondaparinux versus 2/20 lepirudin patients

• New thromboembolic events
  – 14/24 fondaparinux patients versus 19/20 lepirudin patients

Study Outcomes – Grouzi et al.

• Limb amputation
  – 1/24 fondaparinux patients versus 2/20 lepirudin patients

• Venous limb gangrene
  – 1/24 fondaparinux patients versus 2/20 lepirudin patients
  – All occurred before treatment began

• Bleeding complications
  – None

Is Fondaparinux Really Recommended in the 2008 ACCP Guidelines?

• 2C recommendation
  – “Weak recommendation, low or very low quality recommendation”

• “… there is uncertainty whether the usual prophylactic or therapeutic doses of fondaparinux would be effective in a patient with severe HIT-associated hypercoagulability.” – 2008 ACCP Guidelines

• “In summary, fondaparinux has the likely advantage (vs. DTI) of improving bridging to warfarin, but (unlike DTIs) its efficacy as a primary non-heparin anticoagulant for severe HIT-associated hypercoagulability is not established.” – Ted Warkentin

Considerations when using Fondaparinux for HIT

2008 ACCP Guideline Recommendations
• If HIT is unlikely (4 Ts score 0-3), can continue therapeutic dose heparin for patients with “treatment” indication, or give 2.5 mg fondaparinux for patients with “prophylaxis” indication

• Use DTI during initial thrombocytopenic phase then transition to DTI-fondaparinux to avoid DTI-warfarin bridge
  – “In this way, one circumvents the “off-label” use of fondaparinux as the primary treatment of HIT,…” – Ted Warkentin


Bivalirudin

• Advantages
  – Inhibits both circulating and clot-bound thrombin
  – Less expensive than argatroban and lepirudin
  – Has FDA approval for PCI in patients with HIT/HITTS
    • Grade 1B recommendation
  – Short-acting
    • Half-life 25 min (shorter than argatroban and lepirudin)
    • Coagulation normalizes within 60 min after discontinuation

Bivalirudin

• Advantages (continued)
  – Listed as a 2C recommendation in the 2008 ACCP guidelines
    • For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], bivalirudin [Grade 2C]) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA (Grade 1B).
  – Case series and small studies for on- and off-pump cardiac surgery in patients with acute or subacute HIT
    • Grade 1B recommendation
    • Koster et al (largest)


Bivalirudin

• Disadvantages
  – No reversal agent
  – INR effect makes transition to warfarin difficult
  – Cross-reactivity to antilepirudin antibodies
  – Renally cleared and increased half-life in patients with moderate to severe renal dysfunction (3.5 hours)
    • Removed by hemodialysis
  – Limited data outside of PCI and CABG surgery
  – Not FDA approved for HIT/HITT in absence of PCI


Bivalirudin Dosing

• Initial infusion rate 0.15–0.20 mg/kg/h IV
• No initial bolus
• Target aPTT 1.5–2.5 patient’s baseline or mean of laboratory normal range (no initial bolus)

“Best” Data - Kiser et al

- Retrospective study
- Jan 1, 2004 – Mar 31, 2007
- HIT (N=29) or recent history of HIT (N=8)
  - Only 1/5 tested +SRA
  - Only 46% had some + HIT test (17/37)
  - Only 62% had platelet count drop > 50%
- Included patients with renal failure
  - 35% required RRT during admission
- 95% treated in ICU
- Target aPTT was 1.5-2.5 x ULN


Study Outcomes - Kiser et al.

- Thrombosis
  - 10/37 occurred prior to bival
  - 1/37 new DVT
- 8 patient deaths (22%)
  - No patient death secondary to known thrombotic event
- No limb amputations
- Clinically significant bleeding
  - 2/37 patients both requiring discontinuation of bival and transfusion (aPTT within target at time of bleed)
- INR during bival infusion 1.5


Study Outcomes - Kiser et al.

- Bivalirudin median dosing requirements to maintain therapeutic range
  - CrCl > 60 mL/min
    - 0.15 mg/kg/hr
  - CrCl 30-60 mL/min
    - 0.1 mg/kg/hr
    - 33% reduction
  - CrCl < 30 mL/min or receiving RRT
    - 0.03 mg/kg/hr
    - 69% reduction

Is Bivalirudin Really Recommended in the 2008 ACCP Guidelines?

• 2C recommendation
  – “Weak recommendation, low or very low quality recommendation”
• “For bivalirudin (outside the setting of PCI) and fondaparinux, dosing, efficacy, and safety for the management of HIT are not established.”


Ongoing Clinical Trial: Desirudin

• Desirudin is a recombinant hirudin structurally similar to lepirudin
  – Differ by 1/65 amino acids
  – Desirudin is valine-valine and lepirudin is leucine-threonine at N-terminus
  – Desirudin MW = 6.96 KDa while lepirudin MW = 6.98 KDa
  – Antihirudin antibodies also reported following administration
• Subcut desirudin FDA approved for VTE prophylaxis 15 mg BID in THR in US in April 2003 based upon 3 prospective trials
• Available in Europe
• Ongoing clinical trial in patients with suspected HIT comparing
  – Desirudin 15mg subcut in patients without thrombosis and 30mg subcut with thrombosis
  – Argatroban (labeled product dosing)

ClinicalTrials.gov NCT00787332

Summary

• Limited data supporting acute treatment with either fondaparinux or bivalirudin in acute HIT
• Recommendations in 2008 Chest Guidelines 2C for fondaparinux and bivalirudin
• Ongoing clinical trial with DTI desirudin
• There are advantages and disadvantages to each currently recommended treatment for HIT.
• Clinicians should use patient-specific information to select the best therapy.
In a patient admitted to ICU for pneumonia who develops a 60% platelet count drop from baseline, HIT (+ SRA) with new DVT on day 10 of subcut heparin, estimated CrCl 45 mL/min without hepatic disease or congestion, which of the following agents would you recommend as initial therapy (in addition to discontinuing heparin)?

A. Argatroban  
B. Lepirudin  
C. Fondaparinux  
D. Bivalirudin  
E. Warfarin

In a patient admitted for colon resection with a PMH significant for HIT with thrombosis secondary to UFH 6 months ago, which one of the following would you recommend as VTE prophylaxis?

A. Intermittent pneumatic compression  
B. Enoxaparin  
C. Fondaparinux  
D. Subcut lepirudin


Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

SELF-ASSESSMENT QUESTIONS

1. Which of the following has the greatest effect on the INR during transition to warfarin therapy?
   a. Argatroban.
   b. Lepirudin.
   c. Bivalirudin.
   d. Fondaparinux.

2. Which of the following is recommended by the 2008 American College of Chest Physicians guidelines as an initial argatroban dose for a patient with heart failure?
   a. 1 mcg/kg/min.
   b. 2 mcg/kg/min.
   c. Bolus plus 1 mcg/kg/min.
   d. Bolus plus 2 mcg/kg/min.

3. Which of the following agents would be the best choice for anticoagulation during percutaneous coronary intervention in a patient with a history of HIT?
   a. Argatroban.
   b. Lepirudin.
   c. Bivalirudin.
   d. Fondaparinux.

4. Which of the following would you recommend as an anticoagulant during cardiopulmonary bypass for cardiac surgery in a patient with a history of HIT?
   a. Argatroban.
   b. Lepirudin.
   c. Bivalirudin.
   d. Fondaparinux.

Answers
   1. a
   2. a
   3. c
   4. c
Maureen Ann Smythe, Pharm.D.
Clinical Professor of Pharmacy Practice
Wayne State University
Detroit, Michigan
Coordinator of Student and Resident Education
Beaumont Hospital,
Royal Oak, Michigan

Maureen A. Smythe, Pharm.D., FCCP, is a Professor of Pharmacy Practice at the Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University in Detroit, Michigan. She holds a cross appointment as Coordinator of Student and Resident Education with the Department of Pharmaceutical Services at William Beaumont Hospital in Royal Oak, Michigan. Dr. Smythe has established a practice based research program in the area of inpatient anticoagulation.

Previously, Dr. Smythe has held positions of Doctor of Pharmacy Clerkship Coordinator, Associate Professor of Pharmacy Practice (Clinical), and Assistant Professor of Pharmacy Practice (Clinical) at Wayne State University College of Pharmacy & Allied Health Professions located in Detroit, Michigan and Staff Pharmacist at William Beaumont Hospital in Royal Oak, Michigan. She has presented numerous papers nationally and internationally in the area of anticoagulation. She has authored over 100 abstracts and papers. She serves as a reviewer for *Annals Pharmacotherapy, Pharmacotherapy, American Journal Health-System Pharmacy (AJHP)*, and *Critical Care Medicine* and is on the Editorial Board for the *Annals of Pharmacotherapy*. Dr. Smythe had received numerous awards for precepting and teaching.

Dr. Smythe received her Bachelor of Science in Pharmacy and her Doctor of Pharmacy degrees from Wayne State University in Detroit, Michigan. She completed a fellowship in critical care at Henry Ford Hospital in Detroit, Michigan. Dr. Smythe has been a Board Certified Pharmacotherapy Specialist (BCPS) since 1992 and a Fellow of the American College of Clinical Pharmacy since 2000.
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

Maureen Ann Smythe, Pharm.D.

PRESENTATION

Practical Management of Patients with Heparin-Induced Thrombocytopenia

OVERVIEW

Initiation of direct thrombin inhibitor (DTI) therapy requires a careful consideration of factors which may impact dose. Several factors can result in a need to lower the initial dose depending upon the DTI selected. For lepirudin the dose needs to be reduced in the presence of renal dysfunction, dialysis and critical illness. For argatroban the dose needs to be reduced in the presence of hepatic dysfunction, critical illness, anasarca and post cardiothoracic surgery. The transition of a patient with heparin induced thrombocytopenia (HIT) and thrombosis to warfarin must be carefully managed. Warfarin should not be started until after adequate platelet count recovery and it must be overlapped with DTI therapy for a minimum of five days. For patients with isolated HIT (i.e. no thrombosis) the benefit of a short course of warfarin after DTI therapy is uncertain. Patients with a history of HIT should avoid a repeat prolonged exposure to heparin. If cardiac surgery is required heparin can be given intraoperatively if the testing for the HIT antibody yields negative results. An HIT management protocol can help to standardize the management of this clinically significant but infrequent adverse drug reaction.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

• Review dosing of direct-thrombin inhibitor (DTI) therapy in special patient populations.

• Discuss the transition of the DTI therapy to warfarin therapy.

• Summarize the data available on the length of anticoagulant therapy in patients with isolated heparin-induced thrombocytopenia (HIT).

• Outline the considerations in rechallenging a HIT patient with heparin.

• Describe the potential benefit of HIT management protocols.
Learning Objectives

- Review dosing of direct-thrombin inhibitor (DTI) therapy in special patient populations.
- Discuss the transition of the DTI therapy to warfarin therapy.
- Summarize the data available on the length of anticoagulant therapy in patients with isolated heparin-induced thrombocytopenia (HIT).
- Outline the considerations in rechallenging a HIT patient with heparin.
- Describe the potential benefit of HIT management protocols.

<table>
<thead>
<tr>
<th>DTI</th>
<th>Prescribing Info</th>
<th>ACCP Guideline</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>1.5 – 3 x baseline value (not &gt; 100 seconds)</td>
<td>NA</td>
<td>1.5 – 3 x baseline</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>1.5 – 2.5 x median normal</td>
<td>1.5 – 2 x patient’s baseline or mean lab normal</td>
<td>1.5 – 2.5 x baseline or median normal*</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>NA</td>
<td>1.5 – 2.5 x patient’s baseline or mean lab normal</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Initial Lepirudin Dosing in Renal and ICU Patients

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Bolus Dose* (mg/kg)</th>
<th>Infusion (mg/kg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr 1.0 – 1.6 mg/dl</td>
<td>-</td>
<td>0.05 mg/kg/hr</td>
</tr>
<tr>
<td>Scr 1.6 – 4.5 mg/dl</td>
<td>-</td>
<td>0.01 mg/kg/hr</td>
</tr>
<tr>
<td>Scr &lt; 4.5 mg/dl</td>
<td>-</td>
<td>0.005 mg/kg/hr</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.1 mg/kg IV pre-dialysis</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0.005-0.01 mg/kg intermittent IV bolus</td>
<td>0.005mg/kg/hour</td>
</tr>
<tr>
<td>ICU Patient no renal impairment</td>
<td>-</td>
<td>0.05 – 0.1 mg/kg/hr</td>
</tr>
</tbody>
</table>

* In situations of life/limb threatening thrombosis bolus with 0.2mg/kg IV


---

### Initial Argatroban Dosing Recommendations

#### Special Patient Populations

**ACCP Recommendations**

- 0.5 to 1.2 mcg/kg/min for heart failure, MOF, anasarca, post CV surgery

**Renal Impairment**

- Conflicting data

**Hepatic Impairment**

- 0.5 mcg/kg/min (Child Pugh score > 6 or total bilirubin > 1.5mg/dl)

**Obesity**

- Dose on total body weight
  - 1 study in obesity: median starting dose 1mcg/kg/min

Argatroban Dosing & Outcomes in ICU

<table>
<thead>
<tr>
<th>Ref</th>
<th>Initial dose (mcg/kg/min)</th>
<th>N</th>
<th>Major Bleeding</th>
<th>Thrombosis (after Arg)</th>
<th>% HIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>19</td>
<td>0%</td>
<td>0%</td>
<td>26.3</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>17</td>
<td>17.6%</td>
<td>0%</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>38</td>
<td>11%</td>
<td>16% (31% HIT +)</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>34</td>
<td>29%</td>
<td>3%</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>1.14</td>
<td>65</td>
<td>13.6%</td>
<td>16.9%</td>
<td>42</td>
</tr>
</tbody>
</table>

2 studies have shown dose requirements ↓ as # of organ failures ↑


Initial Bivalirudin Dose Requirements

- Not FDA labeled for non PCI HIT
- Clcr > 60ml/min: 0.15 – 0.2 mg/kg/hr
- Clcr 30 – 60 ml/min: 0.08 – 0.1 mg/kg/hr
- Clcr < 30 ml/min: 0.03 – 0.05 mg/kg/hour
- CRRT: 0.03 – 0.05 mg/kg/hr

Warfarin Initiation in HIT

- No warfarin until substantial platelet count recovery, usually at least 150 x 10^9/L
- Initiate with low maintenance doses (maximum 5 mg)
- Continue DTI therapy until:
  - Stable plateau in platelet count
  - INR is in target range
  - Minimum 5 days of overlap with DTI and warfarin
- Can use chromogenic X assay for transition


Chest 2008; 133: 340s – 380s, Chest 2008; 133:141-159
DTI Induced INR Elevation

- A drug lab interaction
- Argatroban clinically significant \( \uparrow \) INR

INR prolongation: argatroban > lepirudin > bivalrudin\(^1\)

- Differing effect related to different molar concentrations in plasma\(^2\)


Conversion of Argatroban to Oral Anticoagulant Therapy

- If INR is \( \leq 4.0 \), continue concomitant therapy
- If INR is \( >4.0 \), stop infusion and repeat INR 4-6 hours later
- INR within therapeutic range on warfarin alone: continue warfarin monotherapy
- INR below therapeutic range on warfarin alone: resume argatroban therapy

Measure INR daily\(^†\)

\(^†\) If arg dose \( > 2 \) mcg/kg/min reduce to 2 mcg/kg/min for 4-6 hrs before checking INR


Chromogenic Factor X Conversion From Argatroban to Warfarin

- Chromogenic factor X measures amount factor X
- Levels of 11 – 42% are inversely correlated with INRs of 2 to 3.5 for warfarin patients
- Levels below 11%: \( \Rightarrow \) INR > 3.5
- Levels above 42%: \( \Rightarrow \) INR < 2
- Benefit: no interruptions in argatroban therapy

How are patients with isolated HIT managed at your institution?

A. Heparin cessation alone  
B. DTI until platelet count recovery then no anticoagulation  
C. DTI until platelet count recovery, then warfarin < 30 days  
D. DTI until platelet count recovery then warfarin > 30 days  
E. Fondaparinux ± DTI initially  
F. None of the above

Frequency of Thrombosis in Isolated HIT

- Patients with isolated HIT identified over 14 year period and records reviewed for 30 days
- 62 patients identified
- Cumulative rate of thrombosis at 30 days was 52.8%
- Management:
  - heparin cessation 58%
  - change to warfarin ~ 34%


New thrombosis in Isolated HIT Patients Managed with DTI Therapy

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>DTI</th>
<th>Incidence New Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAT 1,2,3 Meta-Analysis</td>
<td>Lepirudin</td>
<td>4.4%</td>
</tr>
<tr>
<td>Post-marketing observational study</td>
<td>Lepirudin</td>
<td>2.1%</td>
</tr>
<tr>
<td>ARG 911</td>
<td>Argatroban</td>
<td>8.1%</td>
</tr>
<tr>
<td>ARG 915</td>
<td>Argatroban</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Argatroban trial data includes patients transitioned to warfarin

Rechallenge HIT Patients with Heparin?

HIT does NOT appear to demonstrate typical immune anamnesis

1. In pts with history of HIT, HIT does not occur earlier in those with recent heparin exposure
2. Rapid onset HIT occurs with heparin exposure within last 100 days
3. Median time to antibody negativity is 50 – 85 days
4. HIT patients re-exposed to heparin:
   • antibodies typically do not develop
   • When antibodies develop, same time frame required, same strength of response seen


Proportion of Patients with Heparin-Dependent Antibodies After HIT

<table>
<thead>
<tr>
<th>Days</th>
<th>No. at risk</th>
<th>Antigen assay</th>
<th>Activation assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>93</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>1</td>
<td>92</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>30</td>
<td>14</td>
</tr>
</tbody>
</table>

Copyright © 1996 Massachusetts Medical Society; all rights reserved; Warkentin TE. N Engl J Med. 2001; 344: 1286-1292.
Heparin Rechallenge

• In situations with well defined alternative anticoagulant choices, avoid heparin

• Rechallenge may be needed for cardiac or vascular surgery

• Document antibody negativity, in emergent cases ensure at least 2-3 months have passed since episode of HIT

• Avoid prolonged course of heparin therapy


Cardiac Surgery with History of HIT
ACCP Recommendations

• Antibody negative → UFH Level 1 B

• Antibody negative by PF4 dependent EIA, antibody positive by washed platelet activation assay → UFH Level 2C

Avoid post-operative heparin exposure

PF4 = platelet factor 4, EIA = enzyme immunoassay, UFH = unfractionated heparin

Cardiac Surgery with Acute HIT
ACCP Recommendations

Decreasing Order of Preference

1) Delay surgery until HIT resolves, antibody negative - Level 1 B
2) Bivalirudin for intra-op anticoagulation – Level 1 B
3) Lepirudin for intra-op anticoagulation – Level 2 C
   • ECT is available
   • Normal renal function
   • Low risk of post-op renal dysfunction
4) UFH + epoprostenol – Level 2 C
5) UFH + tirofiban – Level 2 C

Which of the following best describes the status of HIT recognition and management at your institution?

A. No formal protocol for recognition or management
B. Pharmacy Protocol for DTI dosing & monitoring only
C. Protocol for HIT recognition & comprehensive management (DTI dosing, monitoring, conversion to warfarin)
D. None of the above

Why an HIT Management Protocol?

- Under diagnosis is a concern: CATCH registry
  - prospective observational study in 3,536 pts in 48 U.S. hospitals
  - infrequent recognition & evaluation of HIT
  - treatment often delayed

- Over diagnosis is also a concern

Frequency of > 50% serotonin release by EIA optical density

<table>
<thead>
<tr>
<th>Optical Density units</th>
<th>0/304 0%</th>
<th>1/37 2.7%</th>
<th>2/11 18.2%</th>
<th>5/10 50%</th>
<th>33/37 89.2</th>
</tr>
</thead>
</table>


Why an HIT Management Protocol?

- Infrequent ADR, medications used to manage are costly and have risk

- Poor compliance with platelet count monitoring and DTI dosing recommendations

- National Patient Safety Goal 03.05.01 (former 3 E)
  - reduce the likelihood of patient harm associated with anticoagulation therapy

Saxer SB. Am J Health Syst Pharm 2003; 60: 2588-83.
**Provisional diagnosis of HIT**

- >40-50% fall in platelet count between days 4-14 or to < 100x10^9/L on day 1 if receiving recent heparin exposure
- ± Arterial or venous thrombosis
- Other causes of thrombocytopenia excluded

**Management of HIT**

- Stop all forms of heparin
- Start alternative anticoagulant:
  - Immunoassay and/or functional/platelet activation test (send sample to referral laboratory if test is not available)

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**HIT Algorithm**

Adapted from Figure 1: Chong BH, Thromb Haemost 2009; 101: 279-283.

**HIT Algorithm Cont’d**

Adapted from Figure 1: Chong BH, Thromb Haemost 2009; 101: 279-283.

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**Components of an HIT Protocol**

- When to suspect HIT
- Laboratory testing for the heparin PF4 antibody
- Removal of all sources of heparin
- When to initiate DTI therapy

Components of an HIT Protocol

- DTI dosing and monitoring recommendations
  - agent selection, who initiates and adjusts therapy?
  - starting doses, titration nomogram
  - Fondaparinux?
- Interpretation of laboratory test results
- Warfarin reversal
- Lower limb ultrasonography


Components of an HIT Protocol

- Transition to warfarin therapy
  - When, how, in whom?
- Medical record documentation
- Patient education if HIT confirmed

Nomogram Managed Argatroban Therapy vs Individualized Dosing (N = 100)
Therapeutic aPTT ratio with initial dose

Beaumont Resident Project
Melissa Nguyen
Nomogram Managed Argatroban Therapy vs Individualized Dosing (N = 100)

Major Bleeding

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Non-ICU</th>
<th>ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.54</td>
<td>0.38</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Beaumont Resident Project
Melissa Nguyen

Concluding Remarks

- Reduce lepirudin dosing in renal dysfunction, dialysis, and in critical illness
- Reduce argatroban dosing in hepatic dysfunction, critical illness, post CV surgery, and anasarca
- When transitioning to warfarin, overlap DTI therapy with warfarin for at least 5 days
- The optimal duration of anticoagulant therapy in patients with isolated HIT is uncertain
- Avoid prolonged heparin exposure in those with a history of HIT
- A HIT management protocol can standardize care of an infrequent ADR
Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

SELECTED REFERENCES AND RESOURCES


Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

SELF-ASSESSMENT QUESTIONS

1. The initial dose of argatroban must be reduced in patients with multiple organ failure.

2. A HIT management protocol is not recommended since most clinicians are familiar with the management of HIT.
   a. True.
   b. False.

3. BG is a 45 year old male in the hospital with HIT and thrombosis. BG is on lepirudin therapy with a therapeutic aPTT of 60 seconds (45 – 90 seconds). BG’s baseline platelet count was 230 x 10^9/L. BG’s current platelet count is 79 x 10^9/L. The medical resident wishes to transition BG to warfarin therapy at this time. Which of the following is true?
   a. BG should receive an initial warfarin dose of 10 mg.
   b. Warfarin therapy should be delayed until BG’s platelet count rises to > 100 x 10^9/L.
   c. Warfarin therapy should be delayed until BG’s platelet count rises to > 150 x 10^9/L.
   d. Warfarin therapy should be overlapped with lepirudin therapy for 3 days.

4. ML is a 65 year old female with a history of HIT with thrombosis 1 year ago. ML is scheduled to undergo coronary artery bypass graft surgery in 7 days. ML has been tested for the heparin platelet factor 4 antibody with both an antigen test and a functional assay. Both have returned negative. What is the recommended approach for intraoperative anticoagulation in ML?
   a. Unfractionated heparin.
   b. Bivalirudin.
   c. Lepirudin.
   d. Argatroban.

Answers
1. a
2. b
3. c
4. a
Heparin-Induced Thrombocytopenia (HIT)
Clinical Pearls

Clinical Pearl
The 4Ts of HIT
Edith Nutescu, Pharm.D., FCCP

Patient Case
- 70 year-old 4 weeks s/p St. Jude’s mitral mechanical heart valve placement now hospitalized heart failure and *staph aureus* endocarditis. Started on vancomycin, rifampin and gentamicin
- Admitted on warfarin INR 3.0; heparin started on Hospital Day 3 for INR 2.6
- Now hospital day 5 WBC 28K, Temp 102.1, BP 90/70 mmHg.
- No signs of embolization
Platelet Count

- Discharge 4 weeks ago: 210K
- Admit Hospital Day 1: 180K
- Hospital Day 2: 175K
- Hospital Day 3: 178K
- Hospital Day 4: 130K
- Hospital Day 5 (Monday): 98K

- 46% reduction from admission

2 days of heparin therapy

Establishing the Diagnosis

- 4 T’s bedside scoring system:
  - Thrombocytopenia; Timing; Thrombosis, Other causes for TCY
  - High probability 6-8; low 0-3 points
  - Scores 0-3: < 2% chance of + HPF4 antibody
  - Scores 6-8: 21 – 100% chance of + HPF4 antibody


Thrombocytopenia

<table>
<thead>
<tr>
<th>Points: Score 0, 1 or 2 for each of 4 categories</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50% platelet count fall or nadir 20-100K</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>30-50% platelet count fall or nadir 10-15K</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;30% platelet count fall or nadir 10K</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Timing of fall in platelet count or other sequela

<table>
<thead>
<tr>
<th>Points: Score 0, 1 or 2 for each of 4 categories</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset d 5-10 or &lt; 1 d (if heparin exposure within 30 d)</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt; d 10, or timing unclear, or &lt; d 1 with recent heparin exposure</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count fell &lt; d 4 (without recent heparin exposure)</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Other cause for thrombocytopenia

<table>
<thead>
<tr>
<th>Points: Score 0, 1 or 2 for each of 4 categories</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other cause for platelet count fall is evident</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Possible other cause is evident</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Definite other cause is present</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total Point Score = 2

Clinical Diagnosis of HIT
Pretest Probability: the 4 Ts Score

- **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


Management of Suspected HIT

- **Interpret 4T score**
  - Low risk for HIT
    - Continue therapeutic heparin
    - Switch to either fondaparinux or lepirudin for prophylaxis
  - For moderate to high-risk for HIT, start DTI
- **Confirm with laboratory diagnosis**


Clinical Pearl

How should argatroban infusions be adjusted?

Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)
Case

- A 64 year-old patient hospitalized with ischemic stroke and given LMWH DVT prophylaxis has suspected HIT was started on argatroban 2 mcg/kg/min while awaiting results of confirmatory testing.
- The patient has no significant renal disease
- The upper limit of the hospital normal range for aPTT is 30 sec
- The patient's initial aPTT drawn 4 hrs after the infusion started is 110 sec
- What should the new argatroban dose be?

Argatroban Dosing Adjustment

<table>
<thead>
<tr>
<th>Table 1. Standard Nomogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial infusion rate: 2 mcg/kg/min; check aPTT 4 hrs after start of infusion. Admit rate of infusion as follows:</td>
</tr>
<tr>
<td>aPTT (sec)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>≤54</td>
</tr>
<tr>
<td>&gt;54-90 (target)</td>
</tr>
<tr>
<td>≥91-120</td>
</tr>
<tr>
<td>121-140</td>
</tr>
<tr>
<td>≥150</td>
</tr>
</tbody>
</table>

aPTT = Activated partial thromboplastin time.

Argatroban Dosing Adjustment

<table>
<thead>
<tr>
<th>Table 2. Hepato/Critically Ill Nomogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial infusion rate: 0.6 mcg/kg/min; check aPTT 4 hrs after start of infusion. Adjust rate of infusion as follows:</td>
</tr>
<tr>
<td>aPTT (sec)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>≤54</td>
</tr>
<tr>
<td>&gt;54-90 (target)</td>
</tr>
<tr>
<td>≥91-120</td>
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<tr>
<td>121-140</td>
</tr>
<tr>
<td>≥150</td>
</tr>
</tbody>
</table>

aPTT = Activated partial thromboplastin time.

Ansara et al. Argatroban Nomograms

- N=51 patients
- Therapeutic range derived from median of range (22-36 sec in this case)
- aPTTs measured every 3 hrs. until in range in standard nomogram and every 4 hrs. in hepatic/critically ill nomogram
- Dose adjustments of 50% were used if patients required doses lower than 0.2 mcg/kg/min
- Can move between dosing nomograms if more than 3 dosage adjustments up or down in a row
- Caution if using hepatic/critically ill nomogram as only 11.8% therapeutic at 24 hrs. with most (76.5%) supratherapeutic


Clinical Pearl

Why administer Vitamin K if warfarin is on board at the time HIT is diagnosed?

Maureen Ann Smythe, Pharm.D.

1) Warfarin does not inhibit activated clotting factors and does not inhibit thrombin generation

2) Avoid under- dosing of DTI as warfarin ↑ aPTT

Warfarin induced protein C depletion and subtherapeutic DTI dosing can be a set up for venous limb gangrene (VLG)

Warkentin TE. Chest 2008; 133: 340s-380s.
3) ↓ potential for warfarin induced VLG
   • progression to necrosis in limb affected by DVT
   • palpable or doppler identified pulses
   • elevated INR (marker of severe protein C deficiency)