Formulary Flash

Volume 04, Issue 1 January 2004

A PUBLICATION OF THE PHARMACY AND THERAPEUTICS COMMITTEE (P&T) AND THE DEPARTMENT OF PHARMACY

HEPARIN-INDUCED THROMBOCYTOPENIA

An Underreported and Paradoxical Adverse Drug Reaction
Should it be Flagged as an Allergy?

Overview

Heparin is widely prescribed as an effective anticoagulant for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism. It has been estimated that one-third of hospitalized patients – or 12 million patients per year -- receive heparin.[18] Less obvious uses of heparin include the use of heparin flushes, arterial line heparin drips, or heparinized catheters. **To assure appropriate history, all doses and uses of heparin, including heparin flushes, arterial lines and heparinized catheters, should be documented in the medical record**.

Heparin-induced thrombocytopenia (HIT) is a relatively common but under-recognized complication of heparin administration.[13] The paradox stems from the fact that an anticoagulant can trigger a cascade that results in a hypercoagulable state that may result in thrombosis and death.[16] **Every diagnosis of HIT should be reported as an adverse drug reaction.**

Mechanism

Immune-mediated HIT occurs via a multifaceted interaction among heparin, PF4, and platelet membrane Fc receptors. Additionally, heparin-like particles on endothelial cell surfaces may participate in these interactions, also contributing to severe HIT. Heparin and PF4 unite to form a conjugate the body views as an antigen. Antibodies, mostly IgG, react with the heparin-PF4 molecule to form immune complexes. These immune molecules then interact with Fc receptors on platelet membranes, in turn activating platelets and promoting aggregation, premature removal from the circulation, and thrombocytopenia. In response, additional PF4 is released which facilitates continuation of the immune-mediated cycle responsible for severe HIT. Antibody binding, as a result of the PF4-endothelial cell interaction, increases the possibility of life-threatening thrombosis.[1-3, 6]

More Questions

Once the mechanism of HIT was described in the early 1990s, more questions arose. Why are antibodies generated only in a subgroup of patients receiving heparin? Why are antibodies not always pathogenic? What factors contribute to their pathogenicity? It appears that since PF4 is released only during platelet activation, then the extent of platelet activation and endothelial cell activation (determined by the clinical state of the patient) are key factors in progression to clinical HIT. [16]

There is some evidence that IgA or IgM antibodies may be involved (not just IgG). There is also evidence that pre-existing antibodies to other cytokines could become pathogenic when exposed to heparin.[16] **The following is the concluding paragraph of chapter 6 of reference 16**:

> The conditions that permit formation of the molecular PF4-H target antigen for HIT antibodies involve the properties of the heparin used, dose and duration of therapy and the clinical context of the treated patients. Immunoreactive complexes between PF4 and heparin are formed only under certain conditions. Their formation in high concentrations is facilitated if underlying disease favors platelet activation and release. Similar conditions enhance the pathogenicity of the HIT-generated antibodies. These conditions help unravel the apparent random generation of HIT antibodies in heparin-treated patients, as well as the seemingly random occurrence of thrombotic events.

Should HIT be documented as an Allergy?

Minimally, during the admission in which HIT occurs, the chart, the patient, and the bed should have flags or notes or signs that say "NO HEPARIN – including flushes."[19]

Although patients have been given heparin after the HIT titers have dropped and have not experienced problems,[16] **it is the recommendation of the Drug Usage Evaluation Committee and the P&T Committee that "HIT" or "heparin" should be documented on the allergy list of all medical records and computer programs that list medical records.** However, heparin may be given in certain situations if the HIT antibodies are no longer present.[16]

The Following Pages:

Table 1	Getting on the same page Old and New Terminology A Glossary of Terms
HAT	• Heparin-**associated** thrombocytopenia; also called HIT type 1 or non-immune HAT • A non-immune reaction which usually occurs within 48 to 72 hours of administration • No diagnostic test to confirm cause; i.e., not detected by the usual HIT assays[13] • Platelet count usually does not fall below 100,000 & generally returns to within normal limits despite continued therapy[13] • Not associated with thrombotic events • Up to 30% of individuals who receive heparin may experience this reaction[4, 5]
HIT or "Isolated" HIT or HIT without thrombosis	• Heparin-**induced** thrombocytopenia; also called HIT type 2 or immune HIT • Usually occurs 5 to 14 days after initiation of therapy[13] • Seen in 0.3% to 10% of patients receiving unfractionated heparin[4,5] • Incidence appears to be the greatest in orthopedic patients receiving prophylactic doses of heparin for 10-14 days. • Incidence in medicine patients is lower (less than 1% in patients receiving prophylaxis or therapeutic doses of heparin). • Platelet count drop is variable but often profound • Characterized by a paradoxical hypercoagulable state that may be described as transient acquired thrombophilia[15] or a "thrombin storm" [16] • Thrombocytopenia usually resolves within 3 to 7 days of withdrawal of heparin
HITT or **HITTS**	• Heparin-induced thrombocytopenia **with thrombosis** OR heparin-induced thrombocytopenia **with thrombosis syndrome**; a major life and limb threatening complication • Historically described as the "white clot syndrome"[13] (arterial thrombi); now evident that venous thrombi are more common[13] • Seen in 36% to 50% of patients with HIT and a mild thrombocytopenia (platelet count > 100,000)[13] • Seen in as high as 90% of patients with HIT and more severe thrombocytopenia (platelet count < 30,000)[13] • Described as a more severe, protracted form of HIT with evidence of macrovascular thrombus of the extremities, or thrombus-induced end-organ dysfunction (MI, stroke, renal artery thrombosis, bypass graft occlusion, left atrial thrombosis, valvular thrombosis, or pulmonary embolism)[13]
Delayed-onset HIT	• Can develop after discontinuation of heparin and after platelet count recovery[13,16] • Hypercoagulable state can last up to 30 days after stopping heparin[13] • Patients appear to have a high titer of HIT antibodies; this state clinically resembles a transient autoimmune prothrombotic syndrome[16]
Rapid-onset HIT	• A rapid fall in the platelet count – within minutes or hours of starting heparin • Associated with heparin use within the last 100 days – that is, residual heparin antibodies are circulating[16]
Danaparoid	• A low-molecular weight "heparinoid" that was discontinued by the manufacturer in August of 2002 [5]
UFH	• Unfractionated heparin; a heterogeneous group of straight-chain mucopolysaccharides, called glycosaminoglycans • Animal sources: beef (bovine) lung and porcine lung; beef source is more antigenic • More likely to cause HIT antibody formation and clinical HIT than the low-molecular weight heparins
LMWH	• Low-molecular weight heparin; the two agents on formulary are enoxaparin & dalteparin • Less likely to cause PF4 complexes & HIT antibody formation (due to smaller size of the molecules); thus less likely to cause clinical HIT (incidence as high as 0.5%).[16,18] • Must not be used to treat HIT caused by UHF[1-4,6,8,9]; Once an individual has developed HIT, there is greater than 80% cross-reactivity with LMWHs and the antigenic complex.[3]
PF4	• Platelet factor four; an alpha-granule protein[16] • Released into blood during platelet activation along with platelet-derived microparticles [16] • Binds to heparin forming complexes that may neutralize heparin's anticoagulant properties; these complexes (heparin :PF4 or PF4-H called target antigens or neo-antigens) cause the formation of IgG antibodies against them[1-3, 6,16, 18]
Neoantigen	• Also called a "cryptic auto antigen" [16] or a "neoepitope" or a "cryptic epitope"[19] • A complex between an autologous protein (like PF4) and a foreign substance (like heparin) [16] • The structure (and antigenicity) of these complexes depend on the relative concentration of each substance [16] • The formation of these complexes quickly abates when the foreign substance is no longer present [16]
HIT antibodies	• Usually anti heparin:PF_4 complex IgG antibodies or HIT-IgG [16] • 80% of patients with HIT have antibodies of the IgG isotype (others have IgA or IgM or both)[16] • Associated with injury to the epithelium and the release of tissue factor[13] • Promote the platelet activation cascade that results in platelet aggregation, a marked increase in thrombin generation, elevated levels of thrombin-antithrombin complexes, and the formation of thrombi. • Not all HIT antibodies are pathogenic[16] • Become undetectable at a median of 50 to 85 days following the occurrence of HIT, depending on the assay performed[16]
FcλII receptors	• Also called Fc receptors or FcIIa receptors or FcλRIIA receptors • Receptors on the surface of the platelet to which the HIT antibodies attach leading to potent platelet activation and the procoagulant cascade[13]
Venous limb gangrene	• Necrosis of an extremity (that can result in limb loss) associated with the use of warfarin when given without a direct thrombin inhibitor or when warfarin is started too quickly after stopping heparin in the management of HIT[10,11,16] • Characteristic hallmark is a *supra*therapeutic INR (generally >4), which is a surrogate marker for severely reduced protein C[16] • Risk may be higher with higher doses of warfarin, vitamin K deficiency, and factors related to DIC
CISN	• Coumarin-induced skin necrosis or central tissue skin necrosis (of the breast, abdomen, thigh, flank and leg, etc.) [16]
Phlegmasia cerulea dolens	• An inflamed blue painful limb caused by a severe DVT[16] • Rarely progresses to venous limb gangrene unless warfarin is given without a direct thrombin inhibitor[16]
DIC	• Disseminated intravascular coagulation; decompensated DIC is rare in HIT (5-10% of patients with HIT)[16]

Table 2 The Diagnosis of HIT

Both Clinical and Pathological Criteria Should be Present to Ensure a Reliable Diagnosis
(From Chapter 3 and Appendix 1 of reference 16 unless otherwise noted

- Interpretation of a **platelet count drop during or after heparin therapy**
  1. Thrombocytopenia (using standard definition as a platelet count < 150,000/L) is the most common clinical effect of HIT, occurring in 85-90% of patients diagnosed with HIT
  2. A platelet count fall of 50% or greater from baseline can indicate HIT, **even if the platelet count nadir remains above 150,000**/L (indicating that the standard definition may be inadequate, especially in post op patients with HIT whose count may initially rise due to post-op thrombocytosis)
  3. Occasionally, platelet count declines of a lesser magnitude that are attributable to HIT can be associated with thrombotic events.

- The **clinical diagnosis of HIT is based upon the timing of the fall of the platelet count and the exposure to heparin.**
  1. A thrombocytopenic patient whose platelet count fall began between days 5 and 10 of heparin treatment should be considered to have HIT until proven otherwise. The risk of HIT decreases after the 5 – 10 day window passes.
  2. A rapid fall in the platelet count soon after starting heparin is unlikely HIT unless patient has received heparin within the last 100 days.

- Thrombocytopenia with or without thrombosis during heparin therapy does NOT necessarily indicate a diagnosis of HIT
  1. An assay for HIT antibodies by functional or ELISA assay can be helpful for patients in whom there is a clinical suspicion of HIT, based on the temporal features of the thrombocytopenia, or based on the occurrence of new thrombosis during, or soon after, heparin treatment[15]
  2. The inability to demonstrate HIT antibodies using reliable assays means that an alternative diagnosis must be considered

- HIT is associated with a high frequency of **thrombosis** despite discontinuation of heparin with or without substitution of warfarin.
  1. Localization of thrombosis depends on several acute and chronic clinical factors, e.g., the post op state, atherosclerosis, or the location of intravascular catheters in central veins or arteries.
  2. The more unusual or severe the thrombosis, the more likely it is to be caused by HIT

- Other clinical manifestations
  1. Skin lesions either at heparin injection sites or during IV heparin therapy may be a manifestation of HIT[1] (irrespective of the platelet count)
  2. Petechiae and other signs of spontaneous bleeding are not clinical features of HIT (even in severe thrombocytopenia)
  3. Any acute, unexpected systemic reaction (inflammatory, cardiopulmonary, GI, or neurological) occurring 5 to 30 minutes after an IV bolus of heparin should be considered HIT unless proven otherwise. A platelet count should be taken promptly as the reaction is accompanied by an immediate but transient fall in the platelet count.
  4. Heparin resistance is common, but not specific for HIT

Table 3 Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia

Recommendations Of the College of American Pathologists [15]

This information is on-line on the UHS Clinical Intranet. Access it from the UHS Home Page; on the lower left hand portion of the screen in the "Clinical Apps" section, click on DOLS (Directory of Laboratory Services); from that screen click on Laboratory Bulletins and General Information; under "Laboratory Medicine", click on Hematopathology; then click on Activated Partial Thromboplastin Time, heparin, HIT, and direct thrombin inhibitors

Please take the time to read the entire memo dated December 10, 2003 (only portions of the memo regarding HIT are given here). There is important information on the new method to test and report the aPTT test and guidelines for the weight-based dosing of heparin and adjustments based on the aPTT.

Risk assessment for HIT -- depends on the dose and type of heparin used and the patient population:	**Recommended Platelet Count Monitoring for Early Detection of HIT** (Count the first day of heparin as day 0):
1. Patients at highest risk → **a.** post op patients receiving prophylactic or therapeutic doses of UFH	**1. Monitor platelet count every second day from day 4 to day 10**
2. Patients at intermediate risk → **a.** medical / OB patients receiving prophylactic or therapeutic doses of UFH **b.** post op patients receiving prophylactic doses of LMWH **c.** post op patients receiving intravascular catheter flushes with UFH **d.** patients receiving UFH prior to initiating LMWH	2. **Monitor platelet count 2 or 3 times from day 4 to day 10** (may not be practical for outpatients)
3. Patients at low risk → **a.** medical / OB patients receiving prophylactic or therapeutic doses of LMWH **b.** medical patients receiving intravascular catheter flushes with UFH	**3. Routine monitoring is not recommended**

- **Platelet Count Monitoring should be extended beyond day 10 if:**
  1. the platelet count begins to fall unexpectedly during the 4 to day 10 period
  2. heparin therapy is interrupted and restarted because of an intervening surgical or procedural intervention

- **The crucial time period for monitoring "typical-onset" HIT** is between days 4 and 10 after starting heparin, where the highest platelet count from day 4 (inclusive) onward represents the "baseline" level.

- **To identify "rapid-onset" HIT** in patients exposed to heparin in the previous 100 days and who have circulating HIT antibodies, obtain a repeat platelet count **within 24 hours following re-initiation of heparin.**

- **Obtain a platelet count promptly and compare with recent values if:**
  1. **a patient develops thrombosis during or soon after heparin therapy**
  2. **a patient develops an unusual clinical event in association with heparin therapy** (e.g., heparin-induced skin lesions, acute systemic reaction after an IV heparin bolus.

Table 4	Management of HIT
• Immediately discontinue all heparin exposure (including flushes, arterial line heparin drips, and heparinized catheters) • Assess risk of thrombosis • Initiate therapy with argatroban-- (see information in table 7); • Early cessation of heparin alone is not adequate management[13,18] • Do not begin early warfarin without a DTI on board, or before the platelet count is > 100,000/L[1,18] • Do not administer prophylactic platelet transfusions for the treatment of acute HIT[1]	
Adapted from Formulary Jan 2001 SR Deitcher MD[13]	

Table 5	Recommendations for Prevention of HIT
• Obtain a medical history regarding previous exposures to heparin and episodes of heparin-associated adverse events • Monitor platelet counts as recommended in Table 3 • Whenever possible, limit heparin exposure to < 5 days • Initiate warfarin therapy at the start of heparin therapy to minimize duration of heparin exposure in patients requiring long-term anti-coagulation • Avoid all heparin flushes; most protocols have already been changed to "saline only" flushes • Consider LMWH in patients who will require more than 5 days of heparin treatment. • **Report all incidents of HIT as an adverse drug reaction** • Document an "allergy" in the patient's chart as "heparin" or "HIT"	
Adapted from Formulary Jan 2001 SR Deitcher MD[13]	

Table 6	*Lepirudin (Refludan®) –removed from US market in 2012*

Table 7	*Argatroban* *(From package insert – reference 17 – unless otherwise noted*

Overview

- **A synthetic direct thrombin inhibitor derived from L-arginine; marketed in other countries as Novastan® - however because of similarities with other brand names, the drug is marketed in the U.S. as its generic name.**
- **FDA-approved indications:**
  1. **as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT**
  2. **as an anticoagulant in patients with or at risk for HIT undergoing percutaneous coronary intervention**
- **Cost is $697 per 250 mg/2.5 ml vial**
- **Restricted by P&T to patients with H.I.T. and severe renal impairment; use must be prior-authorized by faculty**

Mechanism of Action

- **Reversibly binds to the thrombin active site pocket (free and clot-associated); does not require the co-factor antithrombin III**
- **Inhibits the following thrombin-catalyzed or thrombin-induced reactions**
  1. **activation of coagulation factors V, VII;**
  2. **activation of protein C**
  3. **platelet aggregation**

Standard Dosing for HIT or HITTS

- **Obtain baseline aPTT**
- **If starting shortly after heparin cessation, allow heparin's effect on aPTT to decrease prior to starting argatroban**

P&T has approved dosing guidelines lower than FDA-approved doses. Current guidelines are posted on the Clincal Pathways and Guidelines page, under Anticoagulation

Dosing based on Hepatic Impairment (No adjustment necessary for RENAL impairment)

Preparation and Dilution

- **Dilute solution further with NS or D_5W to a final concentration of 1 mg/ml (by adding 250 mg [2.5 ml] to 250ml bag)**
- **After adding the drug, the bag must be inverted repeatedly for one minute**

Dose adjustments based on aPTT

- **Check aPTT 2 hours after initiation of therapy to confirm that the patients has attained the desired therapeutic range (1.5 to 3 times the baseline value but NOT TO EXCEED 100 SECONDS)**
- **Adjust rate of infusion as clinically indicated, but DO NOT EXCEED rate of 10 mcg/kg/min**

Switching to warfarin

- **Do not initiate therapy with warfarin unless platelet count is > 100,000/L**
- **Warfarin is contraindicated as monotherapy in acute HIT because of the initial prothrombotic effects**
- **Argatroban will prolong the PT and INR beyond that produced by warfarin alone**
- **Do not use a loading dose of warfarin; initiate therapy with the expected daily dose while maintaining argatroban infusion**
- **Measure INR daily**
  - **If INR is ≤ 4, continue concomitant therapy**
  - **If INR is > 4, stop argatroban infusion and repeat the INR 4 to 6 hours later**
    - **If INR is within target range, continue warfarin monotherapy**
    - **If INR is below target range, resume argatroban infusion**

Overdosage

- **No antidote**
- **Stop drug or decrease the rate of infusion**

References

1. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R., et. al. Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001;119:64S-94S.
2. Klinker KP, Harbilas JW, Johns TE. Drug-induced hematologic disorders. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 5th ed. New York: McGraw-Hill; 2002. p.1790-1793.
3. Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. Ann Pharmacother 2002;36:489-503.
4. Coutre S. Heparin-induced thrombocytopenia. In: UpToDate, Rose, BD (ed), UpToDate, Wellesley, MA, 2003. (accessed 10/01/03).
5. Hutchison TA, Shahan DR (eds). DrugDex® System. Greenwood Village, CO: Micromedex, edition expires 12/2003. (accessed 9/30/03).
6. Warkentin TE. Heparin-induced thrombocytopenia: Pathogenesis and management. Br J Haematol 2003;121:535-555.
7. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. Ann Intern Med 2002;136:210-215.
8. Lindhoff-Last E, Nakov R, Misselwitz F, Breddin H, Bauersachs R. Incidence and clinical relevance of heparin-induced antibodies in patients with deep vein thrombosis treated with unfractionated or low-molecular-weight heparin. Br J Haematol 2002;18:1137-1142.
9. Agnelli G, Sonaglia F. Perspectives on antithrombotic agents: From unfractionated heparin to new antithrombotics. Haematologica 2002; 87:757-770.
10. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med 1997;127:804-812.
11. Warfarin (Coumadin®) Package Insert. Bristol-Myers Squibb Company, 2002 June.
12. Dager WE, White RH. Use of lepirudin in patients with heparin-induced thrombocytopenia and renal failure requiring hemodialysis. Ann Pharmacother 2001;35:885-90.
13. Deitcher, SR. Heparin-induced thrombocytopenia: pathogenesis, management, and prevention. Reprint from Formulary 2001; 36:26-41
14. Warkentin TE. Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia. Recommendations of the College of American Pathologists. Arch Pathol Lab Med 2002; 126: 1415-1423
15. Warkentin TE, Greinacher A. *Heparin-Induced Thrombocytopenia,* 2nd edition. 2001
16. Argatroban Package Insert. Smith Kline Beecham 2000
17. Rice L, Nguyen PH, Vann AR. Preventing Complications in Heparin-Induced Thrombocytopenia. Post Graduate Medicine/ Heparin-Induced Thrombocytopenia 2002; 112:85-89
18. Greinacher A. Treatment of Heparin-Induced Thrombocytopenia. Thrombosis and Haemostasis 1999; 82(2) 457-467

Contributors: RCGarcia RPh, S Saldaña PharmD, J Olson MD, Director of Clinical Laboratories, University Health System
Reviewers: P&T members and Cardiovascular subcommittee members [Bertram Joseph MD, Brandi Kelley PharmD, Pam Maxwell PharmD, Ron Mosier RPh, Lynda Wells MD]
Editors: Alexander Shepherd MD, Chairman, P&T Committee, Yolanda Laurel, Director of Pharmacy Services.

Revised: 9/2009, 7/2012, 10/2016