Heparin-Induced Thrombocytopenia: Controversies and Updates

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ABSTRACT

Heparin is the anticoagulant of choice for most clinical needs. Although highly effective, and in use for many decades, adverse effects of heparin exist. Bleeding and heparin-induced thrombocytopenia (HIT) are the two most important side effects of heparin. Here we will discuss HIT. In about 2% of individuals exposed to heparin, antibodies are formed that cause platelet activation and thrombosis. HIT associated thrombosis is particularly devastating as it leads to amputation or death if untreated. Unfortunately, HIT is a difficult diagnosis because its clinical presentation is not always 'textbook'; signs and symptoms can be atypical or masked by other clinical conditions and the diagnostic laboratory tests are not optimal. Research is in progress to improve our understanding of the disease process of HIT. Information gained from these studies is being used to determine which patient populations are at high risk, to develop improved diagnostic tests, and to improve treatment regimens for thrombosis in patients with HIT. The new anticoagulant drugs under development will also be evaluated for their ability to cause/not cause HIT and for their efficacy in the treatment of patients who have developed HIT. Heparin is a highly useful drug with many beneficial characteristics, and it will likely remain the primary anticoagulant in hospitals for years to come. However, with its use one needs to be watchful for HIT.

INTRODUCTION

The clinical management of blood clotting by heparin is well-accepted and heparin is the anticoagulant of choice for most clinical needs. However, as with any drug, adverse effects exist. Heparin-induced thrombocytopenia is an important adverse effect of heparin. HIT represents a unique hypercoagulable state that can result in a spectrum of minor (skin necrosis) to major reactions (blood clotting). It is important to be aware of HIT because of the potential devastating consequences of amputation and death due to thrombosis that it can produce. It is critical that patients with HIT be identified as soon as possible to initiate early treatment. The diagnosis and treatment of HIT can be difficult and complex.

THE DISORDER

HIT is an immune response to heparin treatment. Antibodies formed to a complex of platelet factor 4 (PF4) and heparin have been found in most patients with HIT. PF4 is a protein that is secreted from activated platelets. HIT antibodies bind to platelets causing more platelet activation and more PF4 release. These activated platelets are strongly pro-coagulant and
promote blood clotting. Because they are activated the body will clear them from the circulation, thus resulting in a low platelet count (thrombocytopenia) in patients with HIT.

Because low molecular weight heparins (LMWHs; Lovenox®, Fragmin®) are similar in structure to heparin, they can generate HIT antibodies too. However, patients treated only with LMWH are about 3-times less likely to develop HIT antibodies than patients treated with heparin. Fondaparinux (Arixtra®) is another anticoagulant derived from heparin. Because it has such a small molecular size, it does not appear to generate HIT antibodies.

THE DIAGNOSIS

Patient Characteristics
HIT develops in approximately 2% of all patients exposed to heparin by any route. Occurrence is highest in those given intravenous heparin. However, subcutaneous heparin, heparin in catheter lines, or heparin bonded to devices has also been reported to cause HIT. HIT occurs more often in patients who have had cardiac and orthopedic surgery. Also there is a higher frequency of HIT in patients who are sicker, such as patients in intensive care units or patients with sepsis. A very low platelet count and renal impairment are associated with more severe thrombotic complications.

Patient Symptoms
The typical, distinctive sign of HIT is an unexplained fall in platelet count in a patient receiving heparin treatment. HIT should also be suspected when there is unexplained thrombosis while the patient is under heparin treatment.

Careful monitoring for thrombocytopenia and thrombosis are the primary means for recognition of HIT. HIT is diagnosed when the platelet count decreases to 50% of the patient’s own baseline, falls to less than $100 \times 10^9/L$, or abruptly falls when the patient is on heparin therapy. Other reasons for thrombocytopenia must be excluded.

Symptoms of HIT (thrombocytopenia or thrombosis) typically appear 4-10 days after exposure to heparin. Patients who received heparin within the prior 100 days can have an immediate, rapid-onset HIT when restarting heparin. Delayed-onset HIT has also been observed with symptoms first appearing several days after discontinuation of heparin. Because this may occur after the patient has been discharged home from the hospital, delayed HIT presents a new challenge to health care. The caretaker or patient may be the first to notice symptoms related to a blood clot in the leg (deep vein thrombosis; DVT), the lungs (pulmonary embolism; PE), or what might appear to be a heart attack or stroke (caused from blood clots).

Laboratory Testing
In addition to the platelet count as discussed above, there are specific tests that identify the presence of HIT antibodies.
Immunologic based tests detect antibodies in blood specific to the PF4-heparin complex. Studies have revealed that many more patients exposed to heparin develop these antibodies than the number of patients who go on to develop thrombocytopenia and/or thrombosis from HIT. It is unclear if the antibodies in patients without symptoms of HIT have any clinical relevance.

There are also functional tests for HIT that measure the ability of all HIT antibodies to activate platelets. Although these types of tests would seem to be more relevant to the clinical disorder, they can be negative in patients with thrombocytopenia and/or thrombosis. In addition, these tests are not easy to perform and require specialized laboratories.

**Complexities**
Unfortunately, all patients with HIT do not fit the classical clinical definition as given above. Because HIT often presents in non-characteristic ways, the diagnosis is often difficult. There is no single definition of thrombocytopenia that meets all clinical situations of HIT. Platelet counts do not always decrease to less than $100 \times 10^9/L$, patients can present without thrombocytopenia, there can be a delayed onset, and thrombosis can occur before thrombocytopenia presents. To further complicate the diagnosis of HIT, none of the available laboratory tests are optimal in sensitivity and specificity to HIT antibodies.

**THE TREATMENT**

**Risk of Blood Clots and Need for Anticoagulation**
Patients with HIT have a greater than 30% chance of developing a clinically significant thrombosis. HIT patients experience a spectrum of thrombotic events including both venous and arterial thrombosis, heart attack, PE, and stroke. HIT thrombosis results in a death rate that exceeds 30% and amputation rates as high as 20%.

The treatment for HIT is to remove heparin as soon as possible. However, because the risk for blood clotting is so great the patient with HIT needs to be anticoagulated.

**Recommended Treatments**
Since heparin cannot be used, an alternative non-heparin anticoagulant has to be used. LMWH should not be given as it interacts with HIT antibodies that were pre-formed under heparin treatment allowing the HIT disease to continue.

The US FDA has approved the direct thrombin inhibitors argatroban and lepirudin as the anticoagulant of choice for patients with HIT. Both drugs can successfully prevent and treat HIT thrombosis. Differences in the pharmacologic characteristics between the two drugs need to be considered.
The American College of Chest Physicians (ACCP) has recently published an updated edition of their recommendations for clinical practice guidelines for patients with HIT. Recommendations for dosing argatroban and lepirudin, which supplement the manufactures’ package inserts based on clinical experience, are included.

The ACCP also states that oral vitamin K antagonists (VKAs; warfarin, Coumadin®) should not be used for the initial management of HIT thrombosis but should follow the regimen of the thrombin inhibitor for the long-term anticoagulant treatment. Patients on VKAs at the time of diagnosis of HIT need to have the VKA reversed with vitamin K, then treated with a thrombin inhibitor.

Another thrombin inhibitor bivalirudin, and the factor Xa (FXa) inhibitor fondaparinux, have also been used to manage patients with HIT. A longer lasting derivative of fondaparinux, idraparinux, may also be useful for the prophylactic management of heparin compromised patients for long-term use. It is unlikely that this agent will have any interaction with PF4 or have the potential to generate HIT antibodies.

Patients requiring cardiac surgery, cardiac catheterization, or percutaneous coronary interventions with an ongoing episode of HIT or a history of HIT represent a difficult clinical challenge. This is due to the high level of anticoagulation needed for the procedure, coupled with the patient’s own risk of blood clotting, and the fact that heparin cannot be used. The ACCP provides recommendations for how to anticoagulate these patients with our current options.

It is important to know if a patient has a past history of HIT when anticoagulation requirements arise. A recent history of HIT (less than 100 days prior) could result in complications if heparin were to be used. If HIT had occurred a year or more in the past, the patient may be able to tolerate heparin without incident. However, laboratory tests should be performed prior to intervention.

**Complexities**

HIT is a complex disorder. Patients are at high risk of serious blood clotting, treatment options are new and not as easy to administer as the traditional heparin anticoagulation. Thus, the clinical management of patients with HIT is complicated. These patients are best managed by a clinician experienced with HIT and the new thrombin inhibitor drugs.

**THE FUTURE**

There are numerous unanswered questions with regard to HIT. Some of the current research investigations have been discussed at the July 2008 meeting of the Scientific and Standardization Committee (SSC) on Platelet Immunology of the International Society on Thrombosis and Haemostasis (ISTH). The following summarizes these discussions.
A difference in the frequency of HIT in Western countries and Japan was shown. This could be related to clinical practice or potentially to genetic variations.

Studies re-confirmed the heterogeneity of HIT antibodies, and continue to show different responses between the various immunologic based assays (EIA) including new kits. There is a desire to have the laboratory testing for HIT standardized, but many issues need to be clarified before this can happen.

Further topics related to EIA test included: how to report test results, how to improve test specificity; and how to obtain specificity to clinically relevant HIT antibodies while reducing sensitivity to non-relevant antibodies.

Algorithms for determining treatment with continued heparin or initiation of an alternate anticoagulant based on clinical probability of HIT (low, intermediate, high) combined with lab test results are being discussed.

The use of fondaparinux for the management of HIT thrombosis (without platelet count monitoring) remains under discussion.

The development of new orally active thrombin and FXa inhibitors drugs to substitute for warfarin has proven feasible. These agents do not generate antibodies to PF4 and exhibit no interactions with HIT antibodies. It is likely that patients with a history of HIT can be managed with such agents as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®), although no clinical data is available yet. Since thrombin generation is an important aspect of HIT, treatment of established HIT thrombosis may prove to be preferable with thrombin inhibitor anticoagulants rather than FXa inhibitors that do not block thrombin. The FXa inhibitor drugs may be best used in patients with a history of HIT who require anticoagulation management on an outpatient basis.

Due to the importance of HIT, the US FDA has required that the immunogenic profile of all LMWHs and their generic (biosimilar) versions be provided for review prior to considerations for approval. Because of significant structural differences, different LMWHs may exhibit different interactions with PF4. This would impact the immunologic outcome upon exposure to these drugs in different clinical indications.

Recently both heparin and LMWHs were found to contain an exogenous adulterant, namely over-sulfated chondroitin sulfate (OSCS). Although minor differences between the molecular profile of OSCS and heparin were found, the contaminant interacts strongly with PF4. This suggests that heparin, LMWHs, and other derivatives such as danaparoid, contaminated with OSCS may potentially trigger a strong immunologic response. The long-term consequence of exposure to OSCS remains unknown at this time.

REFERENCES
2. Walenga JM, Jeske WP, Messmore HL. Mechanisms of venous and arterial thrombosis


