INTRODUCTION
A variety of drugs and disorders can cause thrombocytopenia in patients. Heparin-induced thrombocytopenia (HIT) is considered the most common form of drug-induced thrombocytopenia as well as one of the common causes of thrombocytopenia in hospitalized patients. Next to bleeding, HIT is the most significant adverse effect associated with heparin therapy.

Two clinical forms of HIT are generally recognized. Type I (heparin-associated thrombocytopenia) occurs in up to 30% of patients receiving heparin. It is a non–immune-mediated reaction often presenting early to exposure (within one to two days) with an asymptomatic, mild-to-moderate transient decline in the platelet count (rarely below 100,000/mcL) with few complications. Resolution is often spontaneous without discontinuation of therapy (Table 1). Type II (heparin-induced thrombocytopenia) is the more severe immune-mediated reaction and is the focus of this article.

PATHOPHYSIOLOGY AND ETIOLOGY
Heparin alone is not the major antigen target for the body’s antibody response. Heparin is a negatively charged sulfated glycosaminoglycan with high binding affinity for platelet factor-4 (PF4). PF4 is a positively charged, heparin-neutralizing protein contained in platelet alpha granules and a member of the CXC subfamily of chemokines. It is expressed on the surface of some endothelial cells and the platelet cell surface following activation.

When heparin is administered, it binds to PF4, initiating a conformational change that exposes antigenic epitopes, independent of the heparin-binding domain on PF4. The epitopes are recognized by the immune system and promote the formation of anti-heparin PF4 antibodies (HIT antibodies), most frequently immunoglobulin G (IgG). The large, stable heparin–PF4 complex allows the IgG antibodies to cross-link and occupy FcγIIa receptors, found on the cell surface of platelets, thereby activating the platelets and causing further expression of PF4 in a positive feedback loop mechanism (Figure 1).

Platelet activation also causes the release of prothrombotic microparticles, platelet consumption, and thrombocytopenia. Activated platelet aggregation and their removal from circulation are believed to be responsible for thrombocytopenia and thrombosis. The multimolecular antibody complex can also contribute to thrombosis in other ways via interaction with monocytes, producing tissue factor and endothelial injury.

More than 12 million patients and almost one-third of all hospitalized patients receive heparin each year. HIT antibodies develop in up to 50% of patients following exposure to heparin and can continue to circulate for three months or more in approximately 40% of patients.

A widespread myth is that a positive result for HIT antibodies means that a patient has HIT. Actually, heparin–PF4 antibodies are relatively common following heparin exposure and can be nonpathogenic. Clinical HIT can lead to a severely prothrombotic state, occurring in 1% to 5% of patients receiving heparin and accounting for 600,000 cases of HIT annually. Half of these patients, (approximately 300,000) experience complications associated with thrombosis, and 90,000 die.

Generally, the frequency of HIT is dependent on four risk factors:

- duration of heparin use (the risk begins at day 5 and peaks between days 10 and 14)
- type of heparin (bovine unfractionated heparin [UFH] > porcine UFH > low-molecular-weight heparin [LMWH])
- type of patient population (surgical > medical > obstetrical)
- patient’s sex (females > males)

Table 1 Comparison of Heparin-Induced Thrombocytopenia (HIT I and HIT II)

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10% to 20%</td>
<td>2% to 30%</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>1 to 4 days</td>
<td>5 to 10 days</td>
</tr>
<tr>
<td>Typical nadir platelet</td>
<td>100,000/mcL</td>
<td>30,000–55,000/mcL</td>
</tr>
<tr>
<td>Antibody mediated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboembolic sequelae</td>
<td>None</td>
<td>30%–80%</td>
</tr>
<tr>
<td>Hemorrhagic sequelae</td>
<td>None</td>
<td>Rarely</td>
</tr>
<tr>
<td>Management</td>
<td>Observe</td>
<td>Cessation of heparin, alternative anticoagulation, additional therapy</td>
</tr>
</tbody>
</table>

Heparin-Induced Thrombocytopenia

DIAGNOSIS

The diagnosis of HIT is based on both clinical and serological findings. HIT antibody seroconversion, along with thrombocytopenia or other clinical manifestations, such as skin lesions at heparin injections sites or acute systemic reactions (fever, chills, cardiopulmonary distress) after intravenous (IV) bolus administration, are necessary to confirm a positive diagnosis of HIT.13

Clinically, HIT should be first suspected when a patient receiving heparin, typically for 5 to 14 days, experiences an unexplained drop in the platelet count, usually a decline of 50% or more from baseline, along with moderate thrombocytopenia with a median platelet count of 50 to $6 \times 10^9$ cells/L. However, the nadir platelet counts can range anywhere from $15 \times 10^9$ to $150 \times 10^9$ cells/L in 90% of patients.11

Less frequently, thrombocytopenia can present within 24 hours (as in rapid-onset HIT), or it can be delayed by up to 20 days after heparin has been stopped (as in delayed-onset HIT).14 Thrombocytopenia has also been reported with a single administration.15

To aid in the identification of patients with HIT, clinicians can use a pretest probability scoring system known by the simple mnemonic, the “4 T’s” (Table 2).16,17 Each characteristic feature of HIT—such as Thrombocytopenia, Timing, Thrombosis and the absence of oTther explanations—is given a score ranging from 0 to 2. The sum of each component is used to determine a pretest probability score:

- Scores of 3 or below suggest a low probability of HIT; antibodies are unlikely (less than a 5% probability).
- With high scores of 6 or more, the presence of HIT antibodies is more likely (a greater than 80% probability).
- Scores of 4 to 5 indicate possible HIT with potentially other causes; testing for antibodies is the most useful strategy for these patients.

One component of the pretest probability score is the identification of other causes of thrombocytopenia. This is par-

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Table 2 Pretest Probability of HIT: The “Four T’s”

<table>
<thead>
<tr>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>$&gt;50%$ platelet count fall to nadir $\geq 20,000$</td>
<td>$30%$–$50%$ platelet count fall or nadir $10,000$–$19,000$</td>
</tr>
<tr>
<td>Timing of onset of platelet fall (or other sequelae of HIT)</td>
<td>Days 5–10 or $\leq$ day 1 if prior heparin exposure within the last 30 days</td>
<td>$&gt;Day$ 10 or timing not clear (missing platelet counts) $\leq$ day 1 with prior heparin exposure within the last 30–100 days</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus</td>
<td>Progressive or recurrent thrombosis, erythematous skin lesions, or suspected thrombosis (not proven)</td>
</tr>
<tr>
<td>oTther cause(s) of platelet fall</td>
<td>None evident</td>
<td>Possible</td>
</tr>
</tbody>
</table>

---

Figure 1 Pathogenesis of heparin-induced thrombocytopenia. Platelet factor 4 (PF4) contained in platelet alpha granules is expressed on the platelet cell surface (top left). Following administration, heparin binds to PF4; this conformationally modified complex then attaches to anti-heparin/PF4 antibodies (most frequently IgG) at its Fab binding domain (top right). The large heparin–PF4 complex allows the IgG antibodies to cross-link via its Fc portion and occupy FcγIIa receptors, found on the platelets cell surface, thereby activating the platelets and causing further expression of PF4 and release of prothrombotic microparticles (bottom right to left). IgG= immunoglobulin.

particularly important when patients have multiple medical conditions and are taking medications that can confound the presentation and the diagnosis of HIT. Thrombocytopenia can result from many causes, such as disease processes (infection, bone-marrow disease, infection, disseminated intravascular coagulation, splenomegaly) or drugs (chemotherapeutic agents, antibiotics, anticonvulsants) (Table 3).18–22

**LABORATORY CONFIRMATION**

In many instances, the results from highly specific assays used in the laboratory confirmation of HIT lag behind the diagnosis, which is made primarily on clinical grounds. In these cases, decisions are made based on the pretest probability of HIT. In fact, routine testing for HIT antibodies in the absence of clinical features of HIT, such as thrombocytopenia, thrombosis, or heparin-induced skin lesions, is not recommended. Given the often transient nature of HIT antibodies, acute serum or plasma should be used in assays.10

Two fundamental types of assays are used:

- functional: platelet activation or a serotonin-release assay (SRA)
- antigenic: the enzyme-linked immunosorbent assay (ELISA)

Even though no assay has complete 100% sensitivity or specificity, functional and antigenic assays should serve as complementary tests in the diagnosis of HIT.18

**Functional assay.** Platelet-activation assays include the platelet aggregation assay and the much more sensitive test used today, the SRA. Despite the widespread use of the platelet aggregation test, attributable to its simplicity, inexpensiveness, and the ability to yield results in two to three hours, its comparatively low sensitivity (30% to 50%) brings into question its clinical utility.19

The SRA is the gold standard for laboratory confirmation of HIT. Normal donor platelets are radiolabeled with serotonin and are then “washed,” making them very sensitive to activation by HIT serum. The patient’s serum, as well as therapeutic (0.1 U/mL) and high (100 U/mL) concentrations of heparin, is added. A positive result occurs with significant activation at therapeutic levels and an absence of significant effect at high levels. SRA has high sensitivity (90% to 98%) and specificity (above 95% in early phases and 80% to 97% for late-phase platelet declines). Nevertheless, SRA is technically demanding, time-consuming, and not readily available at most institutions.11,18

**ELISA.** For the solid-phase ELISA, complexes of PF4 with either heparin or polyvinyl sulfonate (depending on the test used) are coated on a microtiter plate. The patient’s serum is then added. If antibodies against the PF4 complex are present, they bind, this can be confirmed by adding a second antibody. A negative result strongly rules out the diagnosis of HIT, whereas a positive result should be confirmed with a functional assay. Sensitivity has been noted at greater than 90% and specificity at 95% in early platelet decline and at 50% to 93% in late platelet decline.18 A potential drawback, however, is that antigen assays are likely to detect the presence of clinically insignificant HIT antibodies, which do not have platelet-activating activity.
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effects. Therefore, clinical HIT does not always develop in patients with a positive test result.

The utility of the test can be improved with increased specificity to detect IgG antibodies to the heparin–PF4 complex rather than detecting a combination of IgG/IgA/IgM. In light of a positive ELISA and no confirmatory functional test, the pretest probability (the 4 T’s) consistent with clinical presentation should strengthen the diagnosis of HIT.11,12,18

MANAGEMENT

If the diagnosis of HIT is strongly suspected (often prior to laboratory confirmation), heparin must be discontinued immediately. This includes heparin-bonded catheters and heparin flushes of intravascular catheters, which can occur as incidental exposures despite a clearly written order to discontinue heparin from the medical house staff. Recording “heparin allergy” in the patient’s record and posting signs at the bedside warning against the use of heparin products are other ways to prevent incidental exposures.23

Low-molecular-weight heparin (LMWH) should also be avoided because of its high potential for cross-reactivity with HIT antibodies, even though it is less likely to trigger antibodies than UFH upon initial administration. Because of the high risk of subsequent thrombosis (25% to 50%) that continues up to 30 days after heparin is discontinued, an alternative anticoagulant should be used until platelet counts recover.

Examples include a direct thrombin inhibitor such as lepirudin (Refludan, Bayer), bivalirudin (Angiomax, Ben Venue) or argatroban (Novastan, GlaxoSmithKline), or a factor Xa inhibitor such as danaparoid (Orgaran, Organon) or fondaparinux (Arixtra, GlaxoSmithKline). This recommendation is based on the presence of thrombocytopenia whether or not thrombosis is present.

Optimal alternative agents should differ in their mechanism of anticoagulation. They should lack cross-reactivity with the heparin–PF4 antibodies, should be fast-acting, and should have a short half-life. They should be easy to monitor and should be well tolerated with a low incidence of bleeding risk.

Table 4 summarizes the current American College of Chest Physicians (ACCP) recommendations for the treatment of HIT. Table 5 depicts alternative agents to heparin anticoagulation in the setting of HIT—agents that are currently available in the U.S. The only two agents approved for management of HIT in the U.S. are the direct thrombin inhibitors lepirudin and argatroban.

Table 4 Treatment of Heparin-Induced Thrombocytopenia (HIT)*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recommendation (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly suspected (or confirmed) HIT (with or without thrombosis)</td>
<td>• Discontinue all heparin (UFH or LMWH, flushes)</td>
</tr>
<tr>
<td></td>
<td>• Administer a non-heparin anticoagulant</td>
</tr>
<tr>
<td></td>
<td>○ Lepirudin (1C)</td>
</tr>
<tr>
<td></td>
<td>○ Argatroban (1C)</td>
</tr>
<tr>
<td></td>
<td>○ Bivalirudin (2C)</td>
</tr>
<tr>
<td></td>
<td>○ Fondaparinux (2C)</td>
</tr>
<tr>
<td>Screening for DVT (whether or not clinical evidence is present)</td>
<td>• Routine ultrasonography of lower-limb veins (1C)</td>
</tr>
<tr>
<td>Management of DTI–vitamin K antagonist overlap</td>
<td>• Vitamin K antagonist is not recommended until platelet count has recovered (at least 150 x 10^9/L) (1B)</td>
</tr>
<tr>
<td></td>
<td>• Vitamin K antagonist should be given only during overlapping alternative anticoagulation (minimum five days) and started at a low dose (maximum: 5 mg warfarin) (1B)</td>
</tr>
<tr>
<td></td>
<td>• Alternative anticoagulation should be continued until platelet count has reached stable plateau and the INR has reached the intended target range (1B)</td>
</tr>
<tr>
<td>Reversal of vitamin K antagonist anticoagulation (for patients receiving a vitamin K antagonist at the time of HIT diagnosis)</td>
<td>• Vitamin K should be given (10 mg orally or 5–10 mg intravenously) (1C)</td>
</tr>
<tr>
<td>Prophylactic platelet transfusions (in patients without active bleeding)</td>
<td>• Do not give (2C)</td>
</tr>
</tbody>
</table>

DTI = direct thrombin inhibitor; DVT = deep vein thrombosis; INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.


bin. Lacking any structural similarity with heparin, it therefore does not cross-react with heparin, PF4, or HIT antibodies. It is approved by the Food and Drug Administration (FDA) for the treatment of HIT complicated by thrombosis, but it has also shown efficacy in preventing new thromboses in patients with isolated HIT and with no clinically apparent thromboembolic complications. However, the potential for increased bleeding has prevented approval for other indications such as use in acute coronary syndromes.

Lepirudin treatment is associated with a rapid and sustained increase in platelet counts and a greater than 50% reduction in the rate of death, amputation, and new thrombotic events in patients with HIT when compared with historical controls. In a combined analysis of three prospective observational studies that included 403 patients and 120 historical controls, the combined outcome of death, amputation, and thrombosis at 35 days was lower in the lepirudin patients; however, there was a significantly higher bleeding rate compared with controls (17.6% vs. 5.8%, respectively). Bleeding was the cause of death in 1.2% of these patients.

The current recommended dosing of lepirudin for the acute HIT management is 0.4 mg/kg as an initial bolus, followed by 0.15 mg/kg per hour (up to 110 kg), adjusted to a target activated partial thromboplastin time (aPTT) between 1.5 and 2.5 times the baseline value. Lepirudin has the longest half-life of all the direct thrombin inhibitors (approximately 80 minutes). Lepirudin undergoes renal elimination and, as a result, can accumulate in patients with renal insufficiency. It is also immunogenic in some patients. Approximately 30% to 40% of patients with HIT develop IgG anti-hirudin antibodies, which paradoxically enhance the agent’s anticoagulant effects by impairing renal clearance and causing drug accumulation.

### Table 5 Non-heparin Alternatives for the Treatment of Heparin-Induced Thrombocytopenia (HIT)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapeutic Dose</th>
<th>Clearance</th>
<th>Half-Life</th>
<th>Monitoring</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin</td>
<td>0.4 mg/kg IV bolus (up to 110 kg), followed by 0.15 mg/kg per hour (up to 110 kg)</td>
<td>Renal</td>
<td>80 minutes</td>
<td>• Measure aPTT 2 hours after initiation of therapy and after each dose adjustment&lt;br&gt;• Therapeutic range: 1.5 to 2.5 x baseline (optimal aPTT, &lt;65 seconds)</td>
<td>Bleeding with therapeutic dose in 17.6% of patients; anti-lepirudin antibodies develop in 30% of patients</td>
</tr>
<tr>
<td>Argatroban</td>
<td>2 mcg/kg per minute continuous infusion; maximal infusion: 10 mcg/kg per minute</td>
<td>Hepatic</td>
<td>40–50 minutes</td>
<td>• Measure aPTT 2 hours after initiation of therapy and after each dose adjustment&lt;br&gt;• Therapeutic range: 1.5 to 3 x baseline (&lt;100 seconds)</td>
<td>Bleeding with therapeutic dose in 6% to 7% of patients</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>For PCI: 0.75 mg/kg IV bolus, followed by continuous infusion 1.75 mg/kg per hour for remainder of procedure; infusion may be continued for 4 hours after the procedure or administered as a low-dose infusion (0.2 mg/kg per hour) for an additional 20 hours</td>
<td>Enzymatic (80%) and renal (20%)</td>
<td>25 minutes</td>
<td>Measure ACT 5 minutes after completing IV bolus</td>
<td>Bleeding with dose used in PCI in 2.4% of patients</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Not established for HIT</td>
<td>Renal</td>
<td>17–20 hours</td>
<td>Anti-factor Xa (calibrated to fondaparinux)</td>
<td>Bleeding with doses 2.5–7.5 mg every 24 hours (1.2%–2.7%)</td>
</tr>
</tbody>
</table>

ACT = activated clotting time; aPTT = activated partial thromboplastin time; PCI = percutaneous coronary intervention.

Data from references 13, 23, 26, 30, 33, 34, and 36.
Argatroban (Novastan)

Argatroban, a small synthetic direct thrombin inhibitor derived from L-arginine, is highly selective and reversibly binds to thrombin. Its antithrombotic effects are exerted by its inhibition of thrombin-mediated fibrin formation; activation of coagulation factors V, VII, and XIII; and platelet activation. Argatroban is approved for both preventing and treating HIT with or without associated thrombosis and for promoting anticoagulation in patients with or at risk for HIT who are undergoing percutaneous coronary intervention (PCI).29

Argatroban has several important advantages over other direct thrombin inhibitors. Unlike the hirudin derivatives (lepirudin and bivalirudin), it is not antigenic. It has a rapid onset of action (one to three hours), a short half-life (39 to 51 minutes), a low molecular weight, and a predictable pharmacokinetic dose response; furthermore, argatroban does not interact with or induce heparin-dependent antibodies, and it can inhibit both free and clot-bound thrombin.29

Thrombin bound to fibrin is protected from inactivation, and heparin’s inability to inactivate bound thrombin is instrumental in its limitation to inhibit propagation of venous thrombi and prevent subsequent rethrombosis.30 It is argatroban’s ability to inactivate bound thrombin that is particularly advantageous, and in addition to preventing further thrombotic events, it can also reduce the extension of existing thromboses.

In two prospective, multicenter studies with a total of 722 patients presenting with HIT with or without thrombosis, argatroban therapy was associated with significant reductions in the composite outcome (all-cause mortality, amputation, or new thrombosis) at 37 days, compared with historical controls.

In the ARG-911 study, the incidence of the composite endpoint was reduced in argatroban-treated patients, compared with control subjects with HIT (25.6% vs. 38.8%; P = 0.014) and in those with thrombosis (43.8% vs. 56.5%, P = 0.13).31

In the ARG-915 study, similar significant reductions were noted in the incidence of the composite endpoint in subjects with HIT who received argatroban (28.0% vs. 38.8; P = 0.04) and in subjects who had HIT with thrombosis (41.5 vs. 56.5; P = 0.07).32 Major bleeding events in this study were defined as overt bleeding, associated with a hemoglobin decrease of 2 g/dL or greater, that led to a transfusion of 2 units or more or that was intracranial, retroperitoneal, or into a major prostatic joint. Although the incidence of major bleeding events did not differ significantly between the two groups in either study (5.3% vs. 6.7%), the decrease was still much lower than that for lepirudin.

The recommended initial dose for argatroban is 2 mcg/kg per minute administered as a continuous IV infusion. A baseline aPTT should be obtained before the drug is given and should be re-checked two hours after the initiation of therapy. The dose should then be adjusted until a target aPTT of 1.5 to 3.0 times the baseline value is achieved (in 100 seconds or less). Doses should not exceed 10 mcg/kg per minute.29

Argatroban is metabolized hepatically, and a dose reduction is required for patients with significant liver disease. An approximate four-fold decrease in clearance (in contrast to normal) has been observed, leading to drug accumulation.

The primary parameter used to monitor argatroban therapy is the aPTT, which achieves steady state within one to three hours after therapy begins and which must be monitored carefully. If argatroban is used in a patient with HIT who presents with concomitant moderate hepatic impairment, the recommended initial dose is 0.5 mcg/kg per minute. The dose is titrated until the aPTT at steady state is 1.5 to 3.0 times the baseline level.29 It may also take longer to reverse the anticoagulant effects in these patients. Caution must be taken because, like other direct thrombin inhibitors, argatroban lacks a specific antidote. Unlike the case with lepirudin, renal adjustments are not required for argatroban, which may be a safer alternative in patients with renal impairment.

Bivalirudin (Angiomax)

A small semisynthetic analogue of hirudin, bivalirudin has several benefits when compared with other direct thrombin inhibitors. It is FDA-approved for anticoagulation in patients with or at risk for HIT thrombosis syndrome (HITTS) who are undergoing PCI, but it is not approved for treating HIT in other settings.33 It is intended to be used concomitantly with aspirin, as reflected in its utility in study populations.

Its advantages are that it undergoes dual elimination via a combination of renal clearance (20%) and plasma proteolytic cleavage (80%). Bivalirudin also has a shorter half-life (25 minutes), reduced immunogenicity, and minimal prolongation of the International Normalized Ratio (INR).

The initial recommended dose for bivalirudin is a 0.75-mg/kg IV bolus, followed by a continuous infusion of 1.75 mg/kg per hour for the duration of the PCI procedure. However, lower doses are recommended for pre-PCI dosing in patients with acute coronary syndromes. If necessary, clinicians can choose to continue the initial infusion four hours after PCI at a lower dose of 0.2 mg/kg per hour (up to 20 hours); however, a lower-concentration IV bag of 0.5 mg/ml (instead of the 5-mg/mL concentration used in the initial infusion IV bag) must be prepared.

Bivalirudin has been safely and successfully used in lower doses in patients with combined hepatic and renal failure.34 For patients with renal impairment, activated clotting time should be monitored. The manufacturer does not recommend bolus dose reductions in renal impairment, but the infusion rate should be reduced to 1 mg/kg per hour in patients with a creatinine clearance (CrCl) of less than 30 mL/minute. Bivalirudin is hemodialyzable, and infusion rates for patients receiving hemodialysis should be even lower (i.e., to 0.25 mg/kg per hour).33

Factor Xa Inhibitors

Danaparoid (Orgaran)

Danaparoid is a mixture of glycosaminoglycans derived from porcine intestinal mucosa. Despite the extensive experience with the use of this agent in HIT, the agent’s cross-reactivity potential (approximately 10%) and its long half-life (24 hours) remain major drawbacks.35

Although danaparoid was voluntarily removed from the U.S. market in April 2002, it remains available for the treatment and prevention of HIT in Canada, Europe, New Zealand, Australia, and Japan. Its removal from the market was soon followed by the release of another factor Xa inhibitor, fondaparinux.
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Fondaparinux (Arixtra)

Fondaparinux is a synthetic pentasaccharide that selectively inhibits only factor Xa via highly selective binding (at least 94%) to antithrombin III (ATIII), which subsequently potentiates innate neutralization of factor Xa by ATIII. Fondaparinux does not affect thrombin or platelet activation. It is approved for a broad range of indications: treating and preventing venous thromboembolism (VTE), including VTE prophylaxis after major orthopedic surgery, hip fracture surgery, or abdominal surgery, but is not approved for patients with HIT.36

Although published experience with fondaparinux in HIT is limited, several theoretical advantages make it an attractive alternative for HIT. Fondaparinux does not bind to PF4, in large part because of its structure. Fondaparinux shares a similar structure (namely the same pentasaccharide sequence found on UFH and LMWH), but it contains fewer negatively charged groups and domains necessary for complexation with PF4. These factors contribute to the apparent lack of cross-reactivity that is observed with HIT antibodies and result in fewer cases of HIT, compared with UFH and LMWH. In trials of more than 7,500 patients treated with fondaparinux, there have been no case reports of HIT.37

Fondaparinux also has a rapid onset of action, reaching steady state in approximately three hours. It is easy to administer (by subcutaneous injection rather than by continuous infusion), and it can be given once daily. It has a long half-life (17 to 21 hours) and exhibits 100% bioavailability. Routine monitoring is not required. As a result of the comparative insensitivity of routine coagulation tests such as prothrombin time (PT) and aPTT, fondaparinux is best monitored by measuring anti-factor Xa activity and may be especially useful in those patients with deep-vein thrombosis (DVT), pulmonary embolism (PE), or renal insufficiency. This presents challenges for some institutions, because only fondaparinux can be used in the appropriate calibration of the anti-factor Xa assay and the assay might not be readily available.

If coagulation parameters change significantly or if major bleeding occurs, fondaparinux should be discontinued. This drug undergoes renal elimination, and patients with renal impairment have reduced prolonged total clearance. For the same reason, fondaparinux is contraindicated in patients with severe renal impairment (CrCl below 30 mL/minute). Elderly patients (those older than 75 years of age) and those weighing less than 50 kg also experience reduced clearance and should be monitored more closely.

Adding to the danger of hemorrhage in the setting of excessive dosing or prolonged clearance is the lack of an antidote to reverse anticoagulant effects. In trials, major bleeding occurred in 1.2% to 2.7% of participants, a favorable comparison to the direct thrombin inhibitors.37 Although fondaparinux increases serum transaminase levels in 0.7% to 2.6% of patients, dosing adjustments are not recommended in patients with hepatic insufficiency because of a lack of available data.38

Warfarin (Coumadin)

Oral anticoagulation with warfarin (Coumadin, Bristol-Myers Squibb) is not recommended in the acute phase of HIT and should be postponed until platelet counts have recovered substantially (usually to 150 × 10⁹/L).13 Paradoxically, if warfarin is not used appropriately, it can predispose patients with acute HIT to microvascular thrombosis such as venous limb gangrene and skin necrosis. Affected patients typically have supratherapeutic INRs (above 4.0) that correspond to severe protein C depletion.38

If warfarin has already been started before a HIT diagnosis, reversal with vitamin K should be implemented to reduce the risk of warfarin necrosis and to reduce the possibility of underdosing of the direct thrombin inhibitor because of warfarin’s ability to prolong aPTT when it is used in monitoring these agents.

When platelet counts recover and warfarin can be reinstalled, a minimum five-day overlap with alternative anticoagulation is required and initiated with low maintenance doses at a maximum of 5 mg. Alternative anticoagulation must be given in combination until platelet counts stabilize and the INR is within the therapeutic range for at least two days.

CONCLUSION

Heparin is one of the most widely used and valuable anticoagulants for the treatment and prophylaxis of thrombotic complications. However, its ability to induce severe immunologic reactions upon exposure at any dose (with varying degrees of risk), and its prothrombotic complications present challenges for patients and clinicians. HIT is more common than most perceive it to be and the diagnosis, therefore, can be easily missed.

The diagnosis is made primarily upon clinical presentation, which can vary; HIT can occur early or late, and platelet counts can be within the reference range even after a fall of more than 50%. In patients with multiple medical conditions, the diagnosis can be confounded by medications or disease that can also cause similar manifestations. HIT should be considered in any patient with recent exposure to any type of heparin (UFH or LMWH) and with significant reductions in platelet counts or thrombosis.

Without appropriate treatment, 10% to 20% of patients face losing a limb, and 20% to 30% die as a result of the devastating thrombotic complications.8,39 Other complications include DVT, PE, myocardial infarction, cerebrovascular accidents, skin necrosis, and end-organ damage. In light of the rising use of heparin, its complications and potential atypical presentation require a great deal of vigilance; health care providers should learn to expect the unexpected.

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