Special Considerations with Fondaparinux Therapy: Heparin-Induced Thrombocytopenia and Wound Healing

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Multiple options for anticoagulation therapy are now available, placing an additional responsibility on health care workers for choosing the optimal therapy for each patient. The heparins carry a risk of heparin-induced thrombocytopenia (HIT), an immune-mediated reaction to heparin that may lead to pulmonary embolism and death. Fondaparinux, a new, synthetic pentasaccharide, binds to antithrombin III and potentiates antithrombin III's inhibition of factor Xa. Fondaparinux does not bind to platelet factor 4 and thus is theoretically unable to cause immunoallergic HIT. Unlike low-molecular-weight heparins, fondaparinux does not cross-react in vitro with sera from patients with clinical cases of HIT. These findings suggest that fondaparinux would not lead to formation of HIT antibodies and would not provoke clinical thrombosis in patients who had HIT antibodies because of previous exposure to heparins. To date, no cases of immunoallergic HIT have been associated with fondaparinux use in clinical trials. Anecdotal evidence suggests that fondaparinux eventually may prove to be valuable for preventing and treating thrombosis in patients with HIT. The effect of anticoagulants on wound healing is another consideration when choosing a thromboprophylactic strategy after major surgery. There is evidence that thrombin plays a role in wound healing, but fondaparinux is too small to enable antithrombin III to inhibit thrombin. Thus, fondaparinux may be less likely than a low-molecular-weight heparin to interfere with wound healing.

Key Words: anticoagulation therapy, fondaparinux, heparin-induced thrombocytopenia, wound healing, orthopedic surgery.

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The mechanisms by which a thrombus forms are multifactorial and include interlinked processes involving the plasma and endothelial lining, as well as processes inside endothelial cells. The presence of circulatory stasis, endothelial wall damage, or imbalance between pro- and anticoagulant factors can increase an individual's risk for thrombosis. Several classes of anticoagulants, each with distinct characteristics, are now available for the prevention or treatment of thromboembolic disease.

Because of the multiple choices available, selecting an anticoagulant regimen is no longer a simple task of limited options. The decision is influenced by the subtle differences among agents and a consideration of which factors are influencing thrombosis or risk for bleeding. Fondaparinux, a new anticoagulant, has never been associated with the development of a

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syndrome reminiscent of type 2 (immune-mediated) heparin-induced thrombocytopenia (HIT) and eventually may prove to be useful in preventing or treating thrombosis in patients with that condition. In addition, fondaparinux may be less likely than heparins to interfere with wound healing.

Heparin-Induced Thrombocytopenia

Shortly after what is now called unfractionated heparin (UFH) came into widespread use (in the 1950s), a few cases of arterial thromboembolism in patients who had been treated with heparin were reported.[1] The clots in these cases were soft and pale and consisted largely of fibrin and platelets—hence, the name "white clot syndrome." Because the clots tended to develop a week or 2 after the start of heparin therapy, an immune-mediated cause was suspected.

After measurement of platelet counts became routine (in the 1970s), cases of thrombocytopenia were noticed among patients treated with heparins. Two basic patterns were observed.[2] Some of the patients had mild thrombocytopenia that occurred within the first 4 days of heparin therapy (too early to represent an antibody response to a novel antigen) but rarely caused clinical signs or symptoms and tended to resolve even if the heparin therapy was continued. This condition was called HIT type 1. Other patients, however, had thrombocytopenia that arose 5 or more days after the start of heparin therapy (or earlier in patients previously exposed to heparin) and that, paradoxically, was associated with a prothrombotic state. This immune-mediated form was called HIT type 2. In the following discussion, the term HIT will refer to the type 2 (immune-mediated) form. The presence of thrombus in the setting of HIT has been called HIT thrombosis syndrome (HITTS).

Pathophysiology

Heparin-induced thrombocytopenia arises when a patient's immune system produces antibodies (primarily immunoglobulin [Ig] G) to altered platelet factor 4 (PF4), a protein found in the α granules of platelets. Once exposed to heparin, PF4 undergoes conformational changes, exposing certain cryptic epitopes to which IgG can bind.[3] Once antibody binds to PF4, the IgG Fc region can cross-link the platelet FcγIIa receptors, resulting in platelet activation and the release of procoagulant materials (including PF4) from platelet granules.

The platelet aggregation resulting from platelet activation decreases the number of circulating platelets, thus resulting in thrombocytopenia. Nevertheless, the patient is at high risk for thrombosis because of the platelet aggregation and the procoagulant materials released by the activated platelets. Additional PF4 released from α granules interacts with heparan sulfate strands on the endothelial wall, resulting in changes that allow expression of tissue factor. The binding of altered PF4-IgG complexes to monocytes also leads to further expression of tissue factor, thus promoting thrombus formation.[4]

The typical onset of HIT is 4–10 days after reexposure to UFH or low-molecular-weight heparin (LMWH), occurring within 100 days of the first exposure to heparin.[5, 6] However, patients with recent exposure may develop rapid-onset HIT with reexposure to UFH or LMWH. In such situations, acute systemic reactions such as fever, tachycardia, flushing, headache, chest pain, and cardiac arrest have been observed.[5]

Occasionally, HIT arises several days (mean 9 days, but up to 40 days) after UFH or LMWH therapy is discontinued or persists for several weeks after the therapy is discontinued.[7] These cases of delayed-onset HIT suggest that the HIT antibodies are somehow causing platelet activation, even though heparin is no longer present. One possibility is that the antibodies are reactive against PF4 bound to glycosa-minoglycans on the surface of endothelial cells.[8, 9]

Administration of heparin to a patient with delayed-onset HIT could produce signs that suggest rapid-onset HIT. Consequently, the College of American Pathologists recommends that if thrombosis develops during or soon after heparin therapy, the patient's platelet count should be measured promptly and compared with recent values.[10] A platelet count decrease of 50% or more from baseline may indicate HIT, even if a platelet count nadir greater than 150 x $10^3/mm^3$ remains.[10] Even smaller declines in platelet count have been associated with thrombotic events.[10]

The occurrence of HIT mostly is associated with exposure to UFH but has been reported to occur with LMWH.[11] All heparins are heterogeneous mixtures of glycosaminoglycan polymers from animal tissue. However, the LMWH preparations have a lower molecular weight with a narrower range than that of UFH. The ability of a heparin molecule to bind to PF4 depends on the heparin molecule's chain length and degree of sulfation.[12] Probably because of shorter chain

length, LMWHs are less likely than UFH to result in HIT.[11, 13] However, the cross-reactivity of LMWH with HIT antibodies resulting from UFH treatment is greater than 80%.[14] Thus, LMWHs are relatively contraindicated in patients with HIT.

Patients undergoing cardiovascular or orthopedic surgery may be at particularly high risk for HIT and related thrombosis.[15–17] In patients undergoing orthopedic surgery, the reported frequency of HIT is 1% and 3% when patients receive UFH for 1 and 2 weeks, respectively.[13] New, progressive, or recurrent thrombosis occurs in roughly one third to one half of the patients with proved HIT, with the highest rates associated with lower platelet counts.[8] When left unrecognized and/or untreated, HIT can result in permanent morbidity (including amputation) in 20–30% of cases and a mortality rate of up to 30%.[18]

Complications

Although arterial thromboembolic events were historically the first recognized manifestations of HIT, venous thrombotic events (notably proximal deep vein thrombosis and pulmonary embolism) are more frequently observed.[19] Deep vein thrombosis may lead to potentially lethal pulmonary embolism. Possible long-term consequences include a disfiguring and disabling postthrombotic syndrome (which may cause chronic venous ulceration of the lower limb) or pulmonary hypertension. Documented arterial thromboembolic complications of HIT include lower limb arterial thrombosis, thrombotic stroke, myocardial infarction, aortic thrombosis, mesenteric artery thrombosis, renal artery thrombosis, and vascular graft occlusion.[3]

Diagnosis

Recognition of HIT requires a high index of suspicion. However, even small, easily overlooked exposures to heparin (such as a heparin flush used to clear a catheter) have led to the development of HIT antibodies or have caused or exacerbated thrombosis in patients with antibodies.[8]

The consequences of a missed diagnosis of HIT can be grave. Use of heparin products to treat the thromboembolic complications of unrecognized HIT or failure to provide appropriate alternative anticoagulation in cases of recognized isolated HIT (HIT without evident thrombosis) could make the situation much worse.[20] The diagnosis of HIT should be based on a combination of clinically evident abnormalities (thrombocytopenia with or without thrombosis) with detection of HIT antibodies. However, thrombocytopenia (whether heparin related or not) has many possible causes and is common in hospitalized patients, complicating the ability to provide an accurate diagnosis. Although the platelet count typically decreases in patients with HIT, it might not decrease enough to fit the standard definition of thrombocytopenia (< 150 x 10^3/mm^3) even if the decrease is greater than 50%. Furthermore, most patients with enzyme-linked immunosorbent assay (ELISA) test results positive for the HIT antibody never develop thrombocytopenia or thrombosis.[4]

An iceberg model (Figure 1) often is used to describe the process of diagnosing HIT. The model as a whole represents patients who have had exposure to heparin within the appropriate time frame (i.e., starting at least 5 days previously) and have a positive ELISA result for antibody to the HIT antigen (the heparin-PF4 complex). A subset of the model represents patients who also have positive results from functional assays. These assays (e.g., the platelet aggregation test, ^{14}C-serotonin release assay,

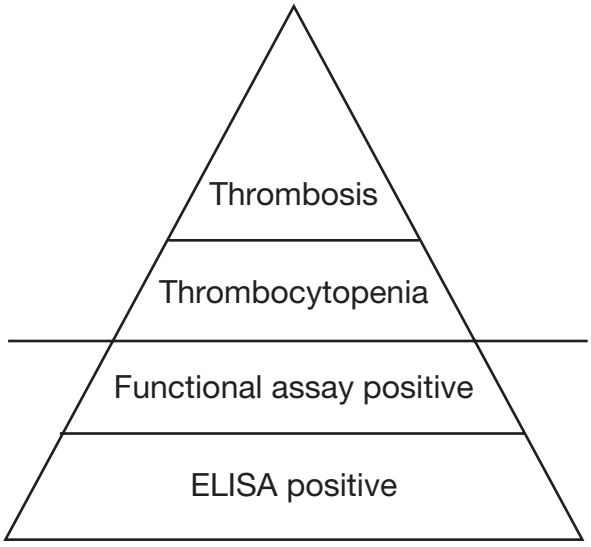

Figure 1. Schematic of the iceberg model of the diagnosis of type 2 heparin-induced thrombocytopenia. The entire model represents patients with positive enzyme-linked immunosorbent assay (ELISA) results. All sections except the bottom section represent patients with positive functional assay results. The portion of the iceberg model above the "waterline" represents patients with thrombocytopenia, with or without thrombosis. (From reference 8 with permission.)

heparin-induced platelet activation assay, and flow cytometry) measure whether patient samples cause activation of platelets from healthy donors in the presence of heparin. The rate of false-positive values can be significant. The subset of the iceberg model above the "waterline" consists of patients who also have a low platelet count. A subset of that portion represents patients who also have thromboembolic complications from HIT.

Management

Heparin should be discontinued immediately in patients with suspected HIT. The LMWHs (e.g., enoxaparin, dalteparin, tinzaparin) are relatively contraindicated and should be avoided. Because of the high risk of thrombosis, especially in the early stages of HIT, alternative anticoagulation should be instituted.[19] The recommended initial treatment for HIT is to remove all sources of heparin and promptly begin therapy with a parenteral direct thrombin inhibitor. Lepirudin and argatroban are approved by the United States Food and Drug Administration for anticoagulation in patients with HIT. Bivalirudin (a shorter-acting direct thrombin inhibitor) is under investigation for that indication. Parenteral direct thrombin inhibitors require careful monitoring of the activated partial thromboplastin time.

When thrombosis is present, warfarin is typically added for long-term anticoagulation. However, warfarin should not be used as a single agent to initiate anticoagulation in patients with HIT because of the risk of venous limb gangrene or other thromboembolic complications. The proposed mechanism is a transient decrease in the levels of the anticoagulant protein C; this decrease, in combination with an existing prothrombotic state, could pose a risk of warfarin-associated skin necrosis (which may lead to the gangrene) or other thromboembolic complications.[8] The risk of these complications can be reduced if the warfarin is begun only after adequate anticoagulation with an agent that prevents thrombin generation or inactivates thrombin (e.g., a direct thrombin inhibitor).[8] The first dose of warfarin should be given only after the platelet count is under recovery.[21] Conservative dosing should be considered, gradually targeting international normalized ratio (INR) values of 2–3 for 5–7 days.[20] This is to avoid excessive INR values, which have been associated with venous limb gangrene in the setting of HIT.[22] Starting warfarin therapy in the setting of HIT is thus a lengthy and costly process that can be further challenging if the direct thrombin inhibitor used causes falsely elevated INR values.

The approach and duration of anticoagulant therapy for patients with isolated HIT has not been specifically studied. Because of concerns about delayed-onset HIT and thrombosis, additional anticoagulation for up to 40 days has been suggested. However, whether this approach leads to improved outcomes has not been determined. Proposed options for extended anticoagulant therapy include warfarin, subcutaneous lepirudin, or fondaparinux.

Fondaparinux

Fondaparinux is a selective, synthetic factor Xa inhibitor and is a synthetic analog of the pentasaccharide sequence that enables heparin to bind to antithrombin III and potentiate its anticoagulant activity. Because fondaparinux has a smaller molecular size and fewer negatively charged sulfoxy groups than those of UFH or LMWH, it does not bind to PF4 and thus is theoretically unable to cause the conformational changes necessary to expose antigenic sites.[23] Unlike LMWHs, fondaparinux does not cross-react in vitro with sera from patients with clinical cases of HIT.[24–26] These findings suggest that fondaparinux would not lead to formation of HIT antibodies and would not provoke clinical thrombosis in patients who had HIT antibodies because of previous exposure to heparins.

To date, no cases of HIT have been observed in any of the more than 7500 patients who have received fondaparinux in clinical trials. In the phase III trials of immediate-phase prophylaxis (up to 11 days after major orthopedic surgery), platelet counts between 100 and 50 x 10^3/mm^3 were observed in 2.9% of fondaparinux-treated patients and counts below 50 x 10^3/mm^3 in 0.2% of fondaparinux-treated patients.[27] However, these cases were clinically indistinguishable from non–immune-mediated (type 1) thrombocytopenia that has been associated with heparin therapy.[27–31] Nearly all of these cases arose during the first 3 days of treatment, and baseline platelet counts below 150 x 10^3/mm^3 were observed in most of the patients with thrombocytopenia.[32] No cases of thrombocytopenia were observed in the 327 patients who received extended prophylaxis (up to 31 days after surgery) with fondaparinux in the Pentasaccharide in Hip-Fracture Surgery Plus

(PENTHIFRA Plus) trial.[33]

The frequency of ELISA test results positive for heparin antibodies in the four orthopedic trials ranged from 2.9–5.5% for fondaparinux and 3.0–3.6% for enoxaparin.[32] However, for most patients (including the one fondaparinux-treated patient with a positive ELISA result and deep vein thrombosis), the thrombocytopenia resolved even though treatment with the study drug was continued.[32] No reference standard assay to detect HIT is available. The ELISA test has a high negative predictive value but produces many false-positive results.[10] The prescribing information[27] specifies that fondaparinux should be discontinued if the platelet count decreases below 100 x 10^3/mm^3. This is out of concern for bleeding related to the lower platelet counts. Many of the cases of thrombocytopenia in major orthopedic surgery trials may have been due to the surgical procedure itself, which can cause platelets to be lost or consumed; thus, the clinical relevance of thrombocytopenia in the fondaparinux clinical trials is unclear.

The prescribing information for fondaparinux states that fondaparinux should be used with caution in patients with a history of HIT.[27] The recent large, multicenter, controlled deep vein thrombosis (MATISSE-DVT)[34] and pulmonary embolism (MATISSE-PE)[35] trials (with more than 2000 patients receiving fondaparinux) showed that a once-daily fixed-dose regimen of fondaparinux was at least as effective and as safe as more complicated regimens of enoxaparin and UFH, respectively, in the early treatment of venous thromboembolism. However, patients with thrombocytopenia (defined as platelet counts < 100 x 10^3/mm^3) at baseline were excluded from these trials. Given the high risk of morbidity and mortality associated with HIT, the use of fondaparinux alone in the initial management of thrombosis due to HIT cannot be recommended over established direct thrombin inhibitor regimens until supportive data are available.

Since fondaparinux has been shown to be effective for thromboprophylaxis and does not interact with PF4, there may be a potential role for fondaparinux in thromboprophylaxis in patients with a recent history of HIT or HITTS. As mentioned, the use of warfarin as a sole agent to initiate anticoagulation in a patient with HIT could pose the risk of warfarin-induced venous limb gangrene.[8] For patients with acute HIT, oral anticoagulant therapy should be delayed until adequate anticoagulation with a rapidly acting parenteral anticoagulant is achieved and, ideally, not administered until there has been substantial platelet count recovery.[8] Fondaparinux may offer a simplified approach with potential economic benefits for continued antithrombotic therapy once the platelet count is under recovery.

Only recently have limited case reports or series describing the use of fondaparinux in the setting of HIT become available, all of which are only in abstract form. One case report involves the successful use of fondaparinux 2.5 mg twice/day in a pregnant woman with HIT (thrombocytopenia, pulmonary embolism, and positive HIT antibodies). After a brief treatment with hirudin, the woman received fondaparinux, without complications, for the duration of the pregnancy. The infant was born healthy, without complications at delivery.[36] Another case involves a patient with a history of lupus anticoagulant, multiple pulmonary embolisms, and acute myocardial infarctions who developed HIT. After another recurrent pulmonary embolism, which initially was managed with lepirudin, the patient was switched to fondaparinux 2.5 mg/day and eventually discharged to receive 2.5 mg alternating with 5 mg, without any further complications during the 8-month period reported.[37]

With regard to initial treatment of HIT, one group reported on five cases of patients with HITTS (ELISA HIT antibody positive) who initially were treated with fondaparinux 7.5 mg/day until successfully transitioned to warfarin.[38] Although these reports are encouraging, the role of fondaparinux (including the correct dose and regimen design) in the prophylaxis and treatment of venous and arterial thrombosis in patients with HIT is unclear. Trials to clarify these points are under way.

Wound Healing

During the past few years, hundreds of published reports of tissue culture and animal models have highlighted the role of thrombin in wound healing. Thrombin has been shown to mediate and enhance wound healing by increasing the production of procollagen connective tissue,[39] causing contraction of collagen matrix,[40] inducing growth factor production, and promoting fibroblast retention.[41, 42] In tissue culture studies, thrombin has been shown to stimulate the growth, replication, and activity of a number of human cellular components of wound healing, including fibroblasts (which are responsible for collagen deposition in wounds[43]), keratinocytes (which

are responsible for dermal repair[44]), myoblasts (which are responsible for muscle repair), and megakeratocytes (which are responsible for the release of growth factor in certain types of wounds[45]). Direct inhibition of thrombin has been shown to reverse many of these effects. Thus, a selective Xa inhibitor may be less likely than a LMWH to interfere with wound healing.

Any delay in the healing of a wound created for implanting a joint prosthesis is of major concern because a sterile environment must be maintained around the implant. Bleeding into a wound or seepage of clear exudate may predispose the patient to infection and increase the length of hospital stay. A recent study of 2001 patients undergoing primary unilateral total knee arthroplasty found that the method of thromboprophylaxis did not affect the amount of postoperative drain output.[46] However, use of LMWH, as opposed to warfarin, resulted in a significantly greater number of patients with actively draining wounds early in the postoperative period.[46] This difference disappeared by the eighth postoperative day. In addition, LMWH was associated with a prolonged time to a dry postoperative wound.[46] In a study of 205 patients undergoing hip fracture surgery, the frequency and severity of wound infection were higher among patients who received LMWH than among those who received mechanical prophylaxis.[47]

Inhibition of factor Xa interrupts the coagulation cascade by preventing the activation of factor II (prothrombin) to form thrombin (factor IIa). Unfractionated heparin and various LMWH preparations inhibit both factor Xa and factor IIa. Fondaparinux selectively inhibits only factor Xa, and even complete inhibition of factor Xa permits some thrombin to be formed through alternative pathways and leaves endogenous thrombin intact. Because fondaparinux does not inhibit thrombin, endogenous thrombin is available to participate in hemostasis and other processes.

Some orthopedic surgeons report that wounds look better and have less drainage in patients who receive fondaparinux instead of the LMWH enoxaparin for postoperative thromboprophylaxis.[48] A prospective study is in progress to evaluate the effect of fondaparinux on wound healing.

Conclusion

In vitro data suggest that fondaparinux does not cause HIT, nor have any cases of HIT been attributed to the use of fondaparinux in clinical trials. Thromboprophylaxis may be necessary for patients with isolated HIT or a history of HIT; fondaparinux's ease of use and lack of cross-reactivity with PF4 could make it an attractive option in that setting. The prescribing information states that fondaparinux should be used with caution in patients with a history of HIT because such use had not been studied in clinical trials.[27] Results from a small number of recently reported cases of fondaparinux therapy in patients with HIT or HITTS are encouraging, but further clinical investigation (which is under way) is needed. Because of the role of thrombin in wound healing, selective Xa inhibition may offer important advantages for thromboprophylaxis after major orthopedic surgery. The effect of fondaparinux on wound healing is being studied.

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