Heparin-Induced Thrombocytopenia

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A 63-year-old man with coronary artery disease who has recently undergone bypass surgery presents with dyspnea. Findings on physical examination are unremarkable. Laboratory testing reveals a platelet count of 86,000 per cubic millimeter, as compared with 225,000 per cubic millimeter at the time of discharge nine days earlier. The results of chest radiography are unremarkable; spiral computed tomography of the chest shows a pulmonary embolism. Heparin-induced thrombocytopenia is suspected. What diagnostic studies are warranted, and how should this patient be treated?

The Clinical Problem

Heparin-induced thrombocytopenia is a life-threatening disorder that follows exposure to unfractionated or (less commonly) low-molecular-weight heparin. Patients classically present with a low platelet count (<150,000 per cubic millimeter) or a relative decrease of 50 percent or more from baseline, although the fall may be less (e.g., 30 to 40 percent) in some patients. Thrombotic complications develop in approximately 20 to 50 percent of patients.

Heparin-induced thrombocytopenia is caused by antibodies against complexes of platelet factor 4 (PF4) and heparin. These antibodies are present in nearly all patients who receive a clinical diagnosis of the disorder and cause disease in animals. However, they are also present in many patients who have been exposed to heparin in various clinical settings but in whom clinical manifestations do not develop.

It is uncertain why complications occur in some patients but not in others.

The time to the onset of thrombocytopenia after the initiation of heparin varies according to the history of exposure. A delay of 5 to 10 days is typical in patients who have had no exposure or who have a remote (more than 100 days) history of exposure. Precipitous declines in platelet counts (within hours) occur in patients with a history of recent exposure to heparin and detectable levels of circulating PF4–heparin antibodies.

Platelet counts seldom drop below 10,000 per cubic millimeter, are rarely associated with bleeding, and typically recover within 4 to 14 days after heparin is discontinued, although recovery may take longer in some patients.

In patients with heparin-induced thrombocytopenia, the thrombotic risk is more than 30 times that in control populations. The risk of thrombosis remains high for days to weeks after discontinuation of heparin, even after the platelet count normalizes.

Atypical manifestations include heparin-induced skin necrosis, venous gangrene of the limbs, and anaphylactic-type reactions after receipt of an intravenous bolus of heparin.

Among 209 patients for whom platelet counts were available before a diagnosis of thrombosis related to heparin-induced thrombocytopenia was made, 40 per-
The incidence of heparin-induced thrombocytopenia is variable and is influenced by the heparin formulation and the clinical context in which heparin is administered (Table 1). Prospective studies have documented an incidence of heparin-induced thrombocytopenia among patients treated with unfractionated heparin that was 10 times the incidence among those receiving low-molecular-weight heparin. Heparin-induced thrombocytopenia develops more frequently in patients being treated with low-molecular-weight heparin who have had a recent exposure to unfractionated heparin (within 100 days) than in those who have not had a recent exposure to unfractionated heparin. Although experience is limited, heparin-induced thrombocytopenia has not been reported in association with the pentasaccharide fondaparinux; however, PF4–heparin antibodies have been detected after treatment with this drug.

The incidence of heparin-induced thrombocytopenia appears particularly high after orthopedic surgery (Table 1) and is higher among surgical patients than medical patients. Heparin-induced thrombocytopenia is uncommon among pediatric patients and obstetrical patients and patients receiving long-term hemodialysis.

**CLINICAL DIAGNOSIS**

Establishing a diagnosis of heparin-induced thrombocytopenia in patients with complicated medical conditions can be challenging. Other causes of thrombocytopenia, such as bacterial infection, drugs other than heparin, and bone marrow disease, should be excluded, and platelet counts should recover after the discontinuation of heparin.

Diagnosing heparin-induced thrombocytopenia in patients who have undergone recent cardiac surgery is particularly difficult, since in such patients the prevalence of heparin-dependent antibodies is high (up to 25 to 50 percent), thrombocytopenia is common, and other medications may be administered that could cause thrombocytopenia. Studies suggest that in patients with heparin-induced thrombocytopenia after cardiopulmonary bypass surgery there is a biphasic pattern of platelet recovery, similar to that in other surgical patients, in which a postoperative rise in the platelet count is followed by a new decline.

**LABORATORY DIAGNOSIS**

When heparin-induced thrombocytopenia is suspected, testing is indicated for heparin-dependent antibodies with the use of serologic or functional assays, or both. Serologic assays are available at most clinical laboratories, and they detect circulating IgG, IgA, and IgM antibodies. Although immunoassays have high sensitivity (greater than 97 percent), their specificity (74 to 86 percent) is
limited by the fact that they also detect PF4–heparin antibodies in patients who do not have heparin-induced thrombocytopenia (Table 1).6,7,30 Thus, the positive predictive value of the immunoassay can be low (range, 10 to 93 percent, depending on the population),30,31 but the negative predictive value is high (greater than 95 percent).30,32 The specificity of serologic testing for clinical disease can be improved if only IgG antibodies are measured,6 but IgG-specific assays are not commercially available.

Functional assays measure platelet activation and detect heparin-dependent antibodies capable of binding to and activating the Fc receptors on platelets. The sensitivity of platelet-aggregation testing is greater than 90 percent at experienced laboratories.18 Its specificity ranges from 77 to 100 percent, depending on the clinical context of the heparin exposure.18,30 An assay measuring the 14C-serotonin release from activated platelets has high sensitivity (88 to 100 percent) and specificity (89 to 100 percent) but is not widely available.6,18,30 Because of the variability in responsiveness among platelet donors to PF4–heparin antibodies, the positive predictive value of functional assays tends to be higher (89 to 100 percent).
percent) than the negative predictive value (81 percent).30

A proposed diagnostic algorithm for patients in whom heparin-induced thrombocytopenia is suspected, based on our clinical experience, is shown in Figure 1. Serologic testing for PF4–heparin antibodies is recommended in patients when the clinical suspicion of heparin-induced thrombocytopenia is high or intermediate, because in such patients, negative results on serologic testing have a high negative predictive value and suggest an alternative diagnosis.6,32 Laboratory testing is not advised when there is a low clinical suspicion of heparin-induced thrombocytopenia.6,30 A difficult scenario occurs when the patient with an intermediate probability of heparin-induced thrombocytopenia has a positive result on serologic testing. In this setting, a functional assay may be helpful, because a positive result would increase the probability of heparin-induced thrombocytopenia.30

MANAGEMENT

The goals of management of heparin-induced thrombocytopenia are to reduce the thrombotic risk by reducing platelet activation and thrombin generation. All sources of heparin, including the heparin solutions that maintain the potency of intravenous lines that are temporarily not in use, should be discontinued when the clinical suspicion of heparin-induced thrombocytopenia is intermediate or high, and alternative anticoagulant therapy should be initiated (Fig. 1). When the clinical suspicion of heparin-induced thrombocytopenia is low, the decision to stop heparin and pursue alternative anticoagulant therapy should be tailored to the patient’s condition.

Patients who have heparin-induced thrombocytopenia should not be treated with low-molecular-weight heparins, since these have high cross-reactivity with circulating PF4–heparin antibodies.18 Warfarin monotherapy in active heparin-induced thrombocytopenia is also contraindicated, on the basis of reports of warfarin-induced skin necrosis and venous gangrene in the limbs.34 Aspirin, the placement of an inferior venacaval filter, or both are not considered adequate therapies.

Treatment of heparin-induced thrombocytopenia requires anticoagulation with one of two classes of anticoagulant agents (Table 2), direct thrombin inhibitors or heparinoids. Three direct thrombin inhibitors are currently available for patients with heparin-induced thrombocytopenia: lepirudin, argatroban, and bivalirudin. These agents directly bind and inactivate thrombin and, unlike heparin, do not require antithrombin. Direct thrombin inhibitors have short half-lives and show no cross-reactivity to heparin.46 Therapeutic dosing is recommended for patients who have isolated thrombocytopenia or heparin-induced thrombocytopenia with thrombosis.

Lepirudin is a recombinant analogue of hirudin, a leech protein (Table 2). Three prospective, observational studies36,40,41 examined lepirudin in 403 patients and 120 historical controls. In a summary analysis of these studies,15 the rate of the combined outcome of death, amputation, and thrombosis at 35 days was lower among those receiving lepirudin than among controls (20.3 percent vs. 43 percent, P<0.001). Separate analyses of these outcomes revealed significant differences in the rate of new thrombotic events but not in rates of death or amputation; however, the studies were underpowered for these end points. Bleeding rates were significantly higher among those receiving lepirudin (17.6 percent) than among controls (5.8 percent), and bleeding was the cause of death in 1.2 percent of the treated patients.15 These observations have led to the reconsideration of the manufacturer’s recommended dosing guidelines, particularly in older patients in whom subclinical renal insufficiency may impair drug clearance.15,35,36

Antibodies to lepirudin develop in approximately 30 percent of patients after initial exposure and in about 70 percent of patients after repeated exposure.15 Because fatal anaphylaxis has been reported after sensitization to lepirudin,42 patients should not be treated with this agent more than once.

Argatroban is a small synthetic compound that binds reversibly to the catalytic site of thrombin. Argatroban was investigated in two prospective, multicenter studies involving a total of 722 patients who have heparin-induced thrombocytopenia.14,43 The combined outcome of death, amputation, and thrombosis at 37 days was significantly lower among those receiving argatroban (34 to 35 percent) than among controls (43 percent).14,43 As with lepirudin, the benefit was seen largely in the reduction of new thromboembolic complications (10 to 14 percent among those receiving argatroban vs. 25 percent among con-
Thrombocytopenia in a patient receiving heparin or LMWH

High or intermediate clinical suspicion of HIT

Discontinue heparin or LMWH; initiate alternative anticoagulant therapy

Low clinical suspicion of HIT

Heparin or LMWH therapy may be continued

Results of immunoassay

Positive with high suspicion of HIT

HIT confirmed

Positive with intermediate suspicion of HIT

Negative with high suspicion of HIT

Negative with intermediate suspicion of HIT

Consider alternative diagnosis

Consider alternative diagnosis; HIT indeterminate

Consider alternative diagnosis; can restart heparin

Positive

HIT likely

Negative

HIT indeterminate

Figure 1. Diagnostic Algorithm to Confirm or Rule Out Heparin-Induced Thrombocytopenia (HIT) in Patients Who Have Not Undergone Bypass Surgery.

Thrombocytopenia can be absolute (platelet count, <150,000 per cubic millimeter) or relative (defined as a decrease in the platelet count of >50 percent from the highest level before the initiation of heparin therapy). The clinical index of suspicion should be based on a temporal association between the start of heparin therapy and the development of thrombocytopenia (typically beginning 5 to 10 days after the start of heparin) or a new thrombosis; the exclusion of other causes of thrombocytopenia (e.g., drugs other than heparin, disseminated intravascular coagulopathy or other consumptive processes, post-transfusion purpura); rebound in the platelet count on discontinuation of heparin; or some combination of these criteria. On the basis of the criteria, the suspicion could be assessed as high when all three criteria are met, intermediate when one or two are met, and low when none are met. Alternatively, the clinical risk can be assessed according to scores based on other criteria. The decision to initiate alternative anticoagulant therapy should be guided by assessment of the patient’s bleeding risk and coexisting conditions. The decision to continue unfractionated heparin or low-molecular-weight heparin (LMWH) should be tailored to the patient. A functional assay is recommended, where clinically available. Antibodies not specific to PF4–heparin may cause HIT. The decision to continue alternative anticoagulant therapy should be individualized.
trols, P<0.05), but was not seen regarding death or amputation.14,43 Rates of serious bleeding did not differ significantly between the two groups.14,43 Antibodies to argatroban have not been reported.

Bivalirudin is another synthetic thrombin inhibitor that has been approved by the Food and Drug Administration for percutaneous coronary intervention in patients who have or are at risk for heparin-induced thrombocytopenia (Table 2). Because of its short half-life, bivalirudin is being

| Table 2. Alternatives to Heparin for the Treatment of Heparin-Induced Thrombocytopenia.9 |
|---------------------------------|----------------|-----------------|-----------------|-----------------|
| Agent                           | Clearance     | Therapeutic Dose | Monitoring            | Adverse Effects        |
| Direct thrombin inhibitors      |               |                 |                  |                  |
| Lepirudin (Refludan, Berlex)†‡   | Renal         | IV, 0.4 mg/kg of body weight (up to 110 kg); IV bolus: followed by 0.15 mg/kg/hr (up to 110 kg) (maximal initial bolus, 44 mg; maximal initial infusion, 16.5 mg/hr) | Measure aPTT 2 hr after therapy started and after each dose adjustment; therapeutic range, 1.5 to 2.5 times the baseline value (optimal aPTT, <65 sec); check baseline PT before switching therapy to warfarin¶ | Bleeding with therapeutic dose in 17.6% of patients; antilepirudin antibodies develop in 30% of patients |
| Argatroban (Novastan, GlaxoSmithKline)†† | Heparic       | 2 μg/kg/min continuous infusion (maximal infusion, 10 μg/kg/min) | Measure aPTT 2 hr after initiation of therapy and after each dose adjustment; therapeutic range, 1.5 to 3 times the baseline value (not to exceed 100 sec); switching to warfarin complicated by baseline prolongation of the PT∥ | Bleeding with therapeutic dose in 6 to 7% of patients |
| Bivalirudin (Angiomax, The Medicines Company)** | Enzymatic (80%) and renal (20%) | For PCI, 0.75 mg/kg IV bolus followed by 1.75 mg/kg/hr for remainder of procedure; infusion may be continued for 4 hr after the procedure or administered as low-dose infusion (0.2 mg/kg/hr) for an additional 20 hr | Measure ACT 5 min after completing IV bolus | Bleeding with dose used in PCI in 2.4% of patients |
| Anti–factor Xa therapy          |               |                 |                  |                  |
| Danaparoid (Orgaran, Diosynth)††| Renal         | IV, 2250 U bolus followed by 400 U/hr for 4 hr, then 300 U/hr for 4 hr, then 150 to 200 U/hr | Not required, but if needed, maintain anti–factor Xa level, 0.5 to 0.8 U/ml | Bleeding with therapeutic dose in 8.1% of patients; cross-reactivity with PF4–heparin antibodies in 3.2% of patients |

* Except where indicated, the guidelines for dosing and monitoring are from the manufacturers of the drugs. Guidelines for therapeutic dosing are for intravenous (IV) infusion, except for bivalirudin, which is used in patients undergoing percutaneous coronary intervention (PCI). The guidelines of the American College of Chest Physicians recommend overlap use of direct thrombin-inhibitor therapy and warfarin therapy for more than 5 days,18 whereas the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology recommends overlap use of direct thrombin-inhibitor therapy and warfarin therapy until the international normalized ratio (INR) is at a therapeutic level for at least 48 hours.19 PT denotes prothrombin time, aPTT activated partial-thromboplastin time, and ACT activated clotting time.

† These drugs have been approved in the United States for the treatment of heparin-induced thrombocytopenia.
‡ Bolus therapy is not advised in older patients or patients with renal insufficiency.24
§ This value is the maximal aPTT recommended by Lubenow et al.36
¶ Therapeutic lepirudin may prolong the baseline PT slightly, but it generally does not interfere with conversion from lepirudin to warfarin therapy. If the PT is prolonged by more than a few seconds, further evaluation should be undertaken before initiating warfarin.
∥ Combined anticoagulant therapy with argatroban and warfarin produces an INR response that is significantly greater than that obtained with warfarin alone. To change from argatroban to warfarin for outpatient anticoagulant therapy, the INR should be monitored daily and, when the INR is greater than 4, the argatroban infusion should be withheld and the INR rechecked to determine whether it is therapeutic.37 An alternative strategy would be to use a chromogenic factor X assay to monitor warfarin therapy while the patient is also receiving argatroban.
** This drug has been approved in the United States for the treatment of patients undergoing percutaneous coronary intervention who have heparin-induced thrombocytopenia or a history of heparin-induced thrombocytopenia.38
†† This drug is not available in the United States.39
investigated as an alternative to heparin for patients with heparin-induced thrombocytopenia who are undergoing cardiopulmonary bypass. Its use in the treatment of heparin-induced thrombocytopenia has not been investigated in clinical trials.

Other Therapies
Another therapy for heparin-induced thrombocytopenia is danaparoid (a mixture of heparan sulfate and dermatan sulfate), which, like heparin, catalyzes antithrombin-mediated inhibition of activated factor X. Danaparoid is not available in the United States, but it is used in Canada, Europe, and Australia. It is the only agent that has been studied in a randomized trial in patients with heparin-induced thrombocytopenia as an alternative antithrombotic agent (as compared with dextran sulfate, an agent used before direct thrombin inhibitors became available). Twenty-five patients were assigned to warfarin plus danaparoid and 17 were assigned to warfarin plus dextran sulfate for at least 72 hours. On the basis of daily clinical assessments, resolution of thrombosis was considered superior with danaparoid, although follow-up imaging was not reported in the study. In a retrospective comparative study of lepirudin and danaparoid, patients with heparin-induced thrombocytopenia (without thrombosis) who received danaparoid at a prophylactic dose were more likely to have a thromboembolic complication than those receiving lepirudin at a therapeutic dose; however, the use of different therapeutic agents limits the value of this observation.

More recently, the experience in 1418 patients who received danaparoid for a variety of indications and with the use of multiple dosing regimens was summarized. New thromboses occurred during 9.7 percent of the treatment episodes, and serious bleeding occurred in 8.1 percent of the patients. The rate of cross-reactivity with heparin (identified on serologic testing and clinical assessment as a new or persistent reduction in the platelet count or new or extended thrombosis, or both) was 3.2 percent (Table 2).

Clinical trials are lacking comparing these agents with one another, and meaningful comparisons of clinical trials of individual agents are not possible because of differences in study design and patient populations. Consequently, the choice of alternative anticoagulant therapy should be tailored to the patient, taking into account the availability of the drug, the patient’s hepatic function and renal function, the need for a surgical procedure, and drug-specific features, such as prior exposure to lepirudin.

Duration of Therapy and Use of Oral Anticoagulants
The duration of alternative anticoagulant therapy and the subsequent use of oral anticoagulants depend on whether the patient has had a thrombotic event. For patients with isolated thrombocytopenia, therapeutic doses of alternative anticoagulants are recommended until the platelet counts recover to a stable plateau, if not to baseline values. Because the risk of thrombosis remains high for two to four weeks after treatment is initiated, consideration should be given to continuing anticoagulant therapy with an alternative agent or warfarin for up to four weeks. Further study is needed to determine the optimal duration of therapy.

For patients who have heparin-induced thrombocytopenia and thrombosis, therapy with an alternative anticoagulant should be followed by a transition to warfarin, but only after platelet counts have recovered to above 150,000 per cubic millimeter. Oral anticoagulants should be initiated at low doses and overlap with a direct thrombin inhibitor for at least 5 days and until the international normalized ratio (INR) is therapeutic for at least 48 hours; these recommendations are based on case reports of warfarin-induced venous gangrene in the limbs, skin necrosis occurring during shorter periods of overlap therapy, or both.

Because direct thrombin inhibitors variably prolong the prothrombin time, clinicians should follow the manufacturer’s guidelines for monitoring warfarin overlap therapy and repeat measurement of the INR after discontinuing the thrombin inhibitor (Table 2).

Areas of Uncertainty
The clinical significance of heparin-dependent antibodies in the absence of thrombocytopenia or thrombosis, which is particularly common in patients who have undergone cardiac surgery, is unknown. At present, no treatment is recommended for patients with positive results on antibody testing without other disease manifestations.
Unlike the duration of the response to most drug-dependent antibodies, the immune response to heparin appears to be transient. PF4–heparin antibodies disappear from the circulation within a median of 85 days. Although there are reports of limited repeated exposure to heparin in patients in whom the antibodies cleared, concern remains regarding repeated exposure to heparin in those who have had heparin-induced thrombocytopenia. Although rigorous data are lacking, patients should receive alternative anticoagulant agents for most indications. For certain procedures, such as cardiac bypass surgery, the use of direct thrombin inhibitors poses a considerable bleeding risk, and it is recommended that patients with a remote history of heparin-induced thrombocytopenia who have negative tests for PF4–heparin antibodies receive anticoagulant therapy with heparin during the procedure, with an alternative anticoagulant agent used postoperatively, if required.18

**GUIDELINES**

The guidelines of the American College of Chest Physicians (ACCP) and the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology for monitoring and management of heparin-induced thrombocytopenia18,19 are generally similar, but they differ with respect to monitoring platelet counts in different patient populations receiving heparin and low-molecular-weight heparin (Table 1). The recommendations presented in this article are in general agreement with those of the ACCP.

**REFERENCES**


**CONCLUSIONS AND RECOMMENDATIONS**

The patient described in the vignette has new thrombocytopenia and had a thromboembolic event several days after heparin exposure during cardiac surgery, a scenario that is highly suggestive of heparin-induced thrombocytopenia. Other causes of thrombocytopenia (medications other than heparin or infection) should be ruled out. Measurement of PF4–heparin antibodies is warranted and is likely to be confirmatory, although it should be recognized that tests for antibodies may be positive in the absence of clinical manifestations of heparin-induced thrombocytopenia. We would treat this patient with a direct thrombin inhibitor until his platelet counts recover, followed by overlap with the initiation of warfarin therapy. Although data are lacking to guide the optimal duration of treatment for thrombosis related to heparin-induced thrombocytopenia, oral anticoagulant therapy should be continued for three to six months. Documentation of heparin-induced thrombocytopenia should be included in the patient’s medical record, and future exposure to heparin should generally be avoided.

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