Anticoagulation in Heparin-Induced Thrombocytopenia: An Ongoing Challenge

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When blood clotting poses a danger to a patient, the most widely used agent for prevention and treatment of this disorder is heparin. Discovered by chance as an anticoagulant in 1916,[1] heparin is used routinely today to stop clot formation in the arteries of patients with cardiovascular disease and in patients who are undergoing open-heart surgery, cardiac revascularization, and coronary angioplasty. Heparin is also used to treat arterial and venous clotting and to prevent the formation of venous clots in patients undergoing hemodialysis or hemofiltration,[2] in various stages of cancer or cancer therapy,[3,4] in patients who require orthopedic surgery or neurosurgery, and in trauma cases.

Unfortunately, despite the use of heparin as an effective anticoagulant, this agent may cause thrombocytopenia in some patients. The resulting condition is called *heparin-induced thrombocytopenia* (HIT), which is a serious adverse effect of heparin therapy. This article reviews the mechanism of action of heparin and the incidence, clinical manifestations, pathophysiology, and treatment of HIT. The antithrombotic agents hirudin and lepirudin are also discussed.

MECHANISM OF ACTION OF HEPARIN

A glycoprotein with a molecular weight of 58,000 daltons, the unfractionated heparin that is used clinically to prevent clot formation is derived largely from the mucous membranes of pigs and the lungs of cattle.[1,5,6] Heparin counteracts clot formation in several ways,[5,7] primarily by blocking thrombin and its enzymatic conversion of fibrinogen into the fibrin that provides the solid matrix for a clot.[4–6,8] In exerting this effect, heparin first binds to antithrombin III (ATIII), a circulating protein whose physiologic function is to prevent spontaneous coagulation by blocking the activity of thrombin.[4,5] This heparin-ATIII complex accelerates the thrombin-blocking effect of ATIII by one thousand fold, rapidly reducing the coagulant activity of thrombin and significantly inhibiting blood clotting.[5,8,9] Following the blockade and inactivation of thrombin, heparin is released from the complex it forms with ATIII and moves on to exert its anticoagulant effect against other molecules of thrombin.[6]

Heparin also obstructs clotting by interfering with other procoagulant effects of thrombin, such as the thrombin-induced activation of clotting factors V and VIII, which normally hastens fibrin formation.[5] The heparin-ATIII complex also increases the neutralizing effect of ATIII on the activated forms of coagulation factors IX, X, XII, and XIII as well as kallikrein, all of which are essential to the ultimate formation of a clot.[4–6,8] Acting through yet another mechanism, heparin also binds to and increases the activity of heparin cofactor II, a glycoprotein that inactivates thrombin independently of ATIII.[5]

HEPARIN-INDUCED THROMBOCYTOPENIA

Incidence

As noted previously, despite its utility, heparin causes thrombocytopenia in 1% to 5% of patients treated with this agent.[3,10] The resulting condition, HIT, is among the most frequent and important complications of drug therapy[10] and is the most frequent type of drug-induced thrombocytopenia.[2,10] In the modern clinical setting, HIT is particularly important because of the expanding indications for heparin therapy and because HIT may have crippling or lethal effects.[3,10]

Mild cases. Although frank thrombocytopenia does not occur in every case of HIT, the condition is always accompanied by a decrease in the platelet count.[6,10] In many cases, HIT is a mild, early, and transitory effect,[11] occurring within the first few days after heparin therapy is initiated.[12] In these cases, which may reflect a direct platelet-activating effect of heparin,[11] the platelet count usually decreases by 10% to 20%.[11] The platelet count rarely declines below 100×10^9/L, and the platelet count may return to normal, even with continuation of heparin therapy.[2,13] Patients with this mild form of HIT generally do not exhibit symptoms.[2] In

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most patients with HIT, the disorder occurs as this type of mild, transient, isolated thrombocytopenia.

Severe cases. In a small percentage of patients, heparin produces severe thrombocytopenia with the risk of acute and potentially fatal arterial and venous thromboembolism.[3,10–12] This more severe form of HIT generally begins 3 to 15 days after initiation of heparin therapy;[2,6] the platelet count decreases to less than $100 \times 10^9/L$[2,3,11] and in some cases to less than $60 \times 10^9/L$ if administration of heparin is continued.[2,11] If heparin is stopped, the platelet count typically rebounds, reentering its normal range within 1 to 10 days.[11] However, any reexposure of the patient to heparin often precipitates a recurrence of HIT, usually within several hours.[2,6]

Clinical Manifestations

HIT occurs independent of the route of heparin administration (regardless if intravenous, subcutaneous, or intramuscular)[6,10] and regardless if heparin is given prophylactically or therapeutically.[6] Although serious bleeding (eg, retroperitoneal, gastrointestinal, intracerebral, postoperative bleeding) may occur in patients with HIT,[6] most patients do not hemorrhage.[6,10,12,13] **Figure 1** illustrates the incidence of various clinical manifestations.

Thrombosis is the most common complication of HIT.[2,6,10–12] Thrombosis occurs independently of the original thrombotic condition for which heparin is being used.[2] Thrombosis may occur in the arteries or veins,[2,11] often at multiple sites[11] and frequently in the form of platelet-rich thrombi, or "white clots."[12] Arterial clots are more likely to occur in patients taking heparin for a cardiovascular disorder,[11] whereas venous clots are more common in patients taking heparin who have recently undergone surgery.[11] Arterial or venous clotting may lead to myocardial infarction, stroke, pulmonary embolism, kidney and other end-organ failure, and ischemia and gangrene requiring limb amputation.[2,10–12] Thrombosis in HIT is always accompanied by a decrease in the platelet count which, in the absence of severe thrombocytopenia, is often recognized only after a thrombotic event.[14] In a 14-year retrospective study of 127 patients who had experienced HIT,[3] the condition was recognized only after a thrombotic event in 65 of the patients, 13 of whom died during their hospitalization.[3] The 62 remaining patients, in whom HIT was recognized after an episode of thrombocytopenia without thrombosis, had a 52.8% risk of thrombosis over the ensuing 30-day period.[3]

Pathophysiology

Formation of an immune complex. Although the pathophysiology of HIT remains unclear, a number of studies have suggested that HIT originates when heparin forms a complex with platelet factor 4 (PF4) and other proteins released by platelets.[2,3,11,12] This immune complex acts as an antigen that triggers the production of immunoglobulin G (IgG) antibodies directed against itself,[12] and the antibodies in turn bind to receptors for IgG (Fcγ receptors) that normally exist on the platelet surface membrane.[2,11] Binding of the antibody activates the platelet to release substances that trigger blood coagulation,[2,3,11] as well as signaling phagocytic cells in the blood to destroy the antibody-coated platelets.[2] Platelet-kinetic studies have supported these events by showing reduced platelet survival in patients with HIT, and studies of the bone marrow have found that the megakaryocytes that give rise to platelets are present in increased numbers in HIT, apparently in an effort to compensate for the accelerated platelet loss.[2] The cascade of events leading to HIT is illustrated in **Figure 2**.

Attack of endothelial cells. The antibodies produced in HIT may also promote coagulation by attacking endothelial cells in the vascular wall.[2,6,11,12] Even in the absence of heparin, these antibodies can prompt cultured endothelial cells to express tissue factor, which initiates the extrinsic pathway to clot formation.[6,10] The antibodies in HIT may also promote clot formation by neutralizing the heparan sulfate that vascular endothelial cells normally produce to prevent coagulation.[6]

Release of ^{14}C-labeled serotonin. Perhaps the greatest support for an antibody-mediated mechanism in HIT is the finding that sera from patients with HIT contain antibodies[15] that trigger the release of ^{14}C-labeled serotonin from normal platelets labeled with this isotope.[10,15] This finding has led to an assay based on ^{14}C-serotonin release for identifying patients with an HIT-related antibody and preventing thrombotic events before they can occur.[15] Platelet aggregation can be stimulated by these antibodies, which can be assessed by in vitro testing; an enzyme-linked immunosorbent assay test has also been developed to detect heparin-associated antibodies in patient blood samples.[10,15,16]

Deficit of other clotting factors. In addition to containing heparin-induced antibodies, the blood of patients with HIT has been found to contain subnormal levels of ATIII, heparin cofactor II, protein C, and various clotting factors during thrombocytopenic or thrombotic episodes.[10] Because the levels of ATIII and heparin cofactor II return to their normal levels after resolution of HIT, it is unlikely that an inherited deficiency of these clot-regulatory substances is the cause of HIT or a contributor to HIT.[10]

Figure 1. The iceberg model of heparin-induced thrombocytopenia. The syndrome ranges from asymptomatic heparin-induced thrombocytopenia–immunoglobulin G seroconversion to disseminated venous and arterial thrombosis. Adapted with permission from Warkentin TE: Recent advances in the management of heparin-induced thrombocytopenia. *ThromboSite Newsletter.* Levittown, PA: Pharmaceutical Information Associates, 1998;1:4. Available at http://www.thrombosite.com/tsnews/tsnews1_1.html. Accessed January 10, 2000.

Treatment

Risk assessment. The finding of HIT-related antibodies is considered an absolute risk for thrombosis and termination of heparin.[12] However, no method currently exists for identifying patients at risk for HIT before heparin is administered,[13] nor is any specific laboratory test available for predicting whether a patient will experience thrombocytopenia alone or thrombocytopenia complicated by thrombosis.[10] Consequently, the risk of HIT must be weighed against the benefit of heparin for each patient in whom anticoagulation with heparin is considered.[13]

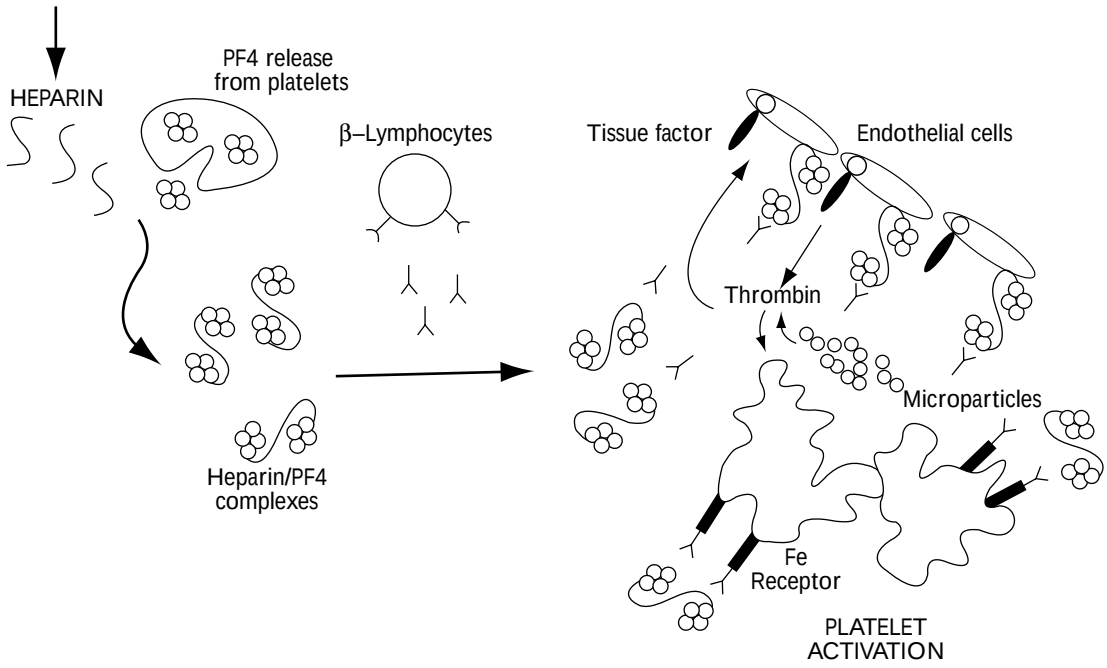

Figure 2. Cascade of events leading to the formation of heparin-induced thrombocytopenia antibodies and prothrombotic components. Fe = iron; PF4 = platelet factor 4. Adapted with permission from Warkentin TE: Recent advances in the management of heparin-induced thrombocytopenia. *ThromboSite Newsletter.* Levittown, PA: Pharmaceutical Information Associates, 1998;1:3. Available at http://www.thrombosite.com/tsnews/tsnews1_1.html. Accessed January 10, 2000.

Minimizing risk. Daily platelet counting and cessation of heparin therapy at a given platelet cutoff level have been recommended for preventing thrombosis in HIT.[6] However, this approach is complicated by a lack of consensus on the appropriate minimum platelet count:[11] Some investigators suggest that heparin therapy should be stopped at a platelet count of 100 to 150×10^9/L, and others suggest significantly different cutoff levels or a decrease of 40% from the patient's pretreatment platelet count as sufficient for terminating heparin.[11] A graph of the platelet count after starting heparin is illustrated in **Figure 3.**

Two equally difficult issues in anticoagulation therapy are choosing a treatment that minimizes the risk of HIT and appropriately managing anticoagulant therapy should be patients who continue to need the therapy after developing HIT. With regard to minimizing the risk of HIT, studies indicate that thrombocytopenia more often accompanies the use of bovine rather than porcine heparin.[2,6] A greater frequency of HIT in patients given unfractionated heparin has also suggested that occurrence of HIT may be reduced by the use of low–molecular weight heparin (LMWH).[2,6,11] In one prospective study, 2.4% of patients treated with LMWH developed HIT-related antibodies compared with 7.4% of patients given unfractionated heparin.[12] However, LMWH can precipitate HIT in patients who have already experienced HIT during treatment with unfractionated heparin.[6]

For patients who develop HIT and require continuing anticoagulant therapy, replacement of heparin with a vitamin K antagonist (eg, warfarin) has been recommended, but only with short-term use of an immediate-acting antithrombotic agent to prevent clotting until the warfarin exerts its effect.[2] However, aspirin, dipyridamole, and dextran have all proven disappointing for short-term coverage.[2]

Antithrombotic agents. Both this problem (ie, patients with HIT who still require anticoagulant therapy) and the limitations of heparin have prompted the quest for a variety of new antithrombotic agents that can reliably exert their effects without inducing HIT.[4] Working toward this goal, the following agents have been investigated:

- **Heparinoids** (eg, danaparoid)—the heparinoids consist of the sulfates of heparan, dermatan, and chondroitin, which react weakly with heparin-induced antibodies[2]

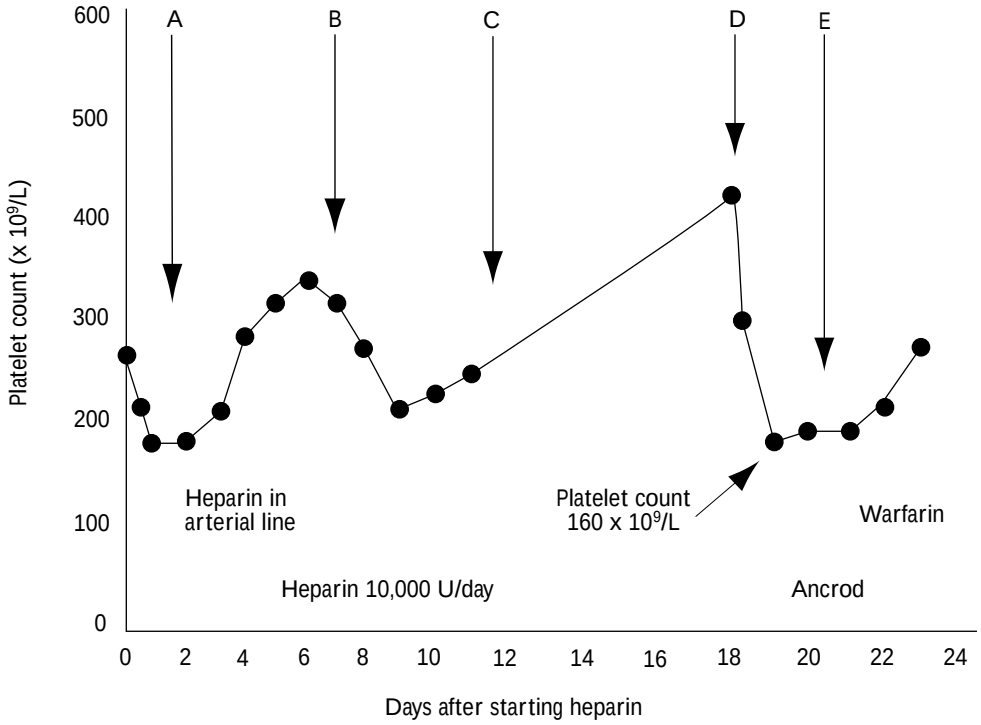

Figure 3. Heparin-induced thrombocytopenia without a platelet count fall to < 150 x 10^9/L. A) Transient postoperative platelet count fall (hemodilution), B) platelet count fall beginning on day seven of heparin use, heparin-induced cytopenia, C) onset of leg pain on day 12, subsequently proven secondary to proximal deep vein thrombosis, D) abrupt falling platelet count (from 429 to 160 x 10^9/L) following two heparin boluses, E) platelet count rise on anticoagulation with ancrod, followed by warfarin. Adapted with permission from Warkentin TE: Recent advances in the management of heparin-induced thrombocytopenia. *ThromboSite Newsletter.* Levittown, PA: Pharmaceutical Information Associates, 1998;1:5. Available at http://www.thrombosite.com/tsnews/tsnews1_1.html. Accessed January 10, 2000.

- **Iloprost**—this analogue of prostacyclin inhibits platelet aggregation[2]
- **Inhibitors of platelet-surface glycoproteins**—these agents prevent glycoproteins from linking platelets to one another and to blood vessel walls to form a clot
- **Ancrod**—this extract of the venom of the Malayan pit viper prevents clotting by chemically cleaving fibrinogen and preventing its conversion into the fibrin that acts as the matrix for a clot[8]

Although none of these agents are currently approved by the United States Food and Drug Administration (FDA) for use in HIT patients, each of these agents has been used in clinical trials or off indication to treat these patients.[16] Clinical data and treatment strategies are available for using danaparoid and ancrod;[16] however, these agents may be difficult to obtain or require sophisticated laboratory support to monitor therapy.

Hirudin. Direct antithrombin agents have been studied as a new approach to anticoagulation as well as alternate anticoagulants when heparin is contraindicated as a result of HIT. Hirudin is an extract from leeches that led to the historic medicinal use of these animals, which, until the discovery of heparin, was the only means of preventing blood coagulation.[14] However, hirudin is not currently approved by the FDA for this indication.

Hirudin is a peptide consisting of 65 amino acids that inhibits clotting by binding directly and specifically to thrombin.[14] Because the mechanism of action for hirudin is different than that for heparin, the risk of thrombocytopenia is minimal.[11] Hirudin has not been recognized to cause significant acute or chronic organ dysfunction.[14,17] The primary adverse effect experienced by patients receiving hirudin is bleeding. Although the anticoagulation is irreversible, the substance has a short half-life when administered to humans and is rapidly cleared renally when discontinued. The potent anticoagulant effect of hirudin has led to the modification and cloning of its gene to produce

recombinant analogues of hirudin as direct antithrombin agents.[14]

Lepirudin. This recombinant analogue of hirudin is the only drug currently approved by the FDA for use as an alternate anticoagulant for preventing clot formation and for treating HIT. Lepirudin is administered intravenously and monitored using the activated partial thromboplastin time. Dose adjustment is necessary in patients with renal insufficiency, and the drug should be given with caution when used in conjunction with thrombolytic therapy.

Studies conducted in Europe of HIT patients treated with lepirudin demonstrate a more rapid recovery of the platelet count and a reduction in the thrombotic complications of HIT compared with historic controls. Bleeding was the most commonly reported adverse effect. More bleeding from puncture sites and wounds was noted with lepirudin as well as an isolated decrease in hemoglobin compared with historic controls; however, the incidence of major bleeding events or intracranial hemorrhage[17] was not significantly increased in patients receiving lepirudin.

SUMMARY

HIT is an uncommon and challenging complication of heparin therapy. Early recognition of the disorder and prompt discontinuation of heparin in any form of HIT is an important first step in management. In patients who require ongoing anticoagulation, several approaches have been tried with success. Direct antithrombin therapy with lepirudin has been approved by the FDA for this condition and may help to limit complications. However, devising the best strategy for treatment of HIT is an evolving process. **HP**

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REFERENCES

1. Kessler CM, Bell WR: Antithrombotic therapy. In *Fundamentals of Clinical Hematology,* 2nd ed. Spivak JL, ed. Hagerstown, MD: Harper & Row, 1984:383.
2. Chong BH: Heparin-induced thrombocytopenia. *Br J Haematol* 1995;89:431–439.
3. Warkentin TE, Kelton JG: A 14-year study of heparin-induced thrombocytopenia. *Am J Med* 1996;101:502–507.
4. Weitz J: New anticoagulant strategies: current status and future potential. *Drugs* 1994;48:485–497.
5. Gravlee G: Anticoagulation for cardiopulmonary bypass. In *Cardiopulmonary Bypass: Principles and Practice.* Gravlee GP, Davis RF, Utley JR, eds. Baltimore: Williams & Wilkins, 1993:340–380.
6. Warkentin TE, Kelton JG: Heparin-induced thrombocytopenia. *Prog Hemost Thromb* 1991;10:1–34.
7. Moorman RM, Zapol WM, Lowenstein E: Neutralization of heparin anticoagulation. In *Cardiopulmonary Bypass: Principles and Practice.* Gravlee GP, Davis RF, Utley JR, eds. Baltimore: Williams & Wilkins, 1993.
8. Bell GH, Emslie-Smith D, Paterson CR: *Textbook of Physiology and Biochemistry,* 9th ed. New York: Churchill Livingstone, 1976:260.
9. Carola R, Harley JP, Noback CR: *Human Anatomy and Physiology.* New York: McGraw-Hill, 1990:523.
10. Boshkov LK, Warkentin TE, Hayward CP, et al: Heparin-induced thrombocytopenia and thrombosis: clinical and laboratory studies. *Br J Haematol* 1993;84:322–328.
11. Fondu P: Heparin-associated thrombocytopenia: an update. *Acta Clin Belg* 1995;50:343–357.
12. Greinacher A: Antigen generation in heparin-associated thrombocytopenia: the nonimmunologic type and the immunologic type are closely linked in their pathogenesis. *Semin Thromb Hemost* 1995;21:106–116.
13. Greinacher A: Heparin-associated thrombocytopenia. *Biomedical Progress: Clinical Trends in Coagulation and Fibrinolysis* 1994;7:53–56.
14. Markwardt F: The development of hirudin as an antithrombotic drug. *Thromb Res* 1994;74:1–23.
15. Nand S, Wong W, Yuen B, et al: Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. *Am J Hematol* 1997;56:12–16.
16. Warkentin TE, Chong BH, Greinacher A: Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemost* 1998:79:1–7.
17. Refludan™ (lepirudin (rDNA) for injection) prescribing information. Hoechst Marion Roussel, Kansas City, MO, 1998.

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