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.5,8,8 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 therapy10 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.1,3,10

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.2,11 Patients with this mild form of HIT generally do not exhibit symptoms.2 In

Dr. Hassell is Associate Professor of Medicine, Division of Hematology, University of Colorado Health Sciences Center, Denver, CO.
administration of heparin is continued. If heparin is being used, Thrombosis may occur in the arteries or original thrombotic condition for which heparin is only after a thrombotic event. In a 14-year retrospective of severe thrombocytopenia, is often recognized by a decrease in the platelet count which, in the absence of severe thrombocytopenia, is often recognized by a decrease in the platelet count, reentering its normal range within 1 to 10 days. However, any reexposure of the patient to heparin often precipitates a recurrence of HIT, usually within several hours.

Clinical Manifestations

HIT occurs independent of the route of heparin administration (regardless if intravenous, subcutaneous, or intramuscular) and regardless if heparin is given prophylactically or therapeutically. Although serious bleeding (eg, retroperitoneal, gastrointestinal, intracerebral, postoperative bleeding) may occur in patients with HIT, most patients do not hemorrhage. The antibodies in HIT may also promote clotting in HIT may also promote coagulation by attacking endothelial cells in the vascular wall. 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. The antibodies in HIT may also promote clot formation by neutralizing the heparan sulfate that vascular endothelial cells normally produce to prevent coagulation.

Release of ¹⁴C-labeled serotonin. Perhaps the greatest support for an antibody-mediated mechanism in HIT is the finding that sera from patients with HIT contain antibodies that trigger the release of ¹⁴C-labeled serotonin from normal platelets labeled with this isotope. This finding has led to an assay based on ¹⁴C-serotonin release for identifying patients with an HIT-related antibody and preventing thrombotic events before they can occur. 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.

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. 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.
Multiple thrombosis (white clot syndrome) occurs in 0.01%–0.1% of cases
- Endothelial cell activation by heparin-induced thrombocytopenia-immunoglobulin G
- Occurrence of disseminated intravascular coagulation
- Possible role of autoreactive platelet-activating immunoglobulin G

Isolated thrombosis occurs in 30% to 80% of the following cases:
Thrombosis may depend on unrelated clinical factors:
- Arterial thrombosis
  - Atherosclerosis
  - Recent vascular trauma (e.g., vascular catheters)
- Venous thrombosis
  - Postoperative immobility
  - Venous limb gangrene
  - Warfarin treatment

Asymptomatic thrombocytopenia occurs in 30% to 50% of the following cases:
Risk of thrombocytopenia may depend on:
- Heparin dose
- Function of patient platelet Fc receptors
- Variable definition of thrombocytopenia

Heparin-induced thrombocytopenia-immunoglobulin G seroconversion occurs in 0% to 10% of cases
Frequency of seroconversion may be related to:
- Degree of sulfation/length of heparin chains
- Dose/mode of administration of heparin

---


**Treatment**

**Risk assessment.** The finding of HIT-related antibodies is considered an absolute risk for thrombosis and termination of heparin. However, no method currently exists for identifying patients at risk for HIT before heparin is administered, nor is any specific laboratory test available for predicting whether a patient will experience thrombocytopenia alone or thrombocytopenia complicated by thrombosis. Consequently, the risk of HIT must be weighed against the benefit of heparin for each patient in whom anticoagulation with heparin is considered.
Minimizing risk. Daily platelet counting and cessation of heparin therapy at a given platelet cutoff level have been recommended for preventing thrombosis in HIT. However, this approach is complicated by a lack of consensus on the appropriate minimum platelet count: 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. 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 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. 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). In one prospective study, 2.4% of patients treated with LMWH developed HIT-related antibodies compared with 7.4% of patients given unfractionated heparin. However, LMWH can precipitate HIT in patients who have already experienced HIT during treatment with unfractionated heparin.

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. However, aspirin, dipyridamole, and dextran have all proven disappointing for short-term coverage.

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. 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.
Iloprost — this analogue of prostacyclin inhibits platelet aggregation.

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.

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. Clinical data and treatment strategies are available for using danaparoid and ancrod; 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. 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. Because the mechanism of action for hirudin is different than that for heparin, the risk of thrombocytopenia is minimal. Hirudin has not been recognized to cause significant acute or chronic organ dysfunction. 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 conjunctivision 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 hemorrhage17 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.

ACKNOWLEDGEMENT

The author received a grant from Hoechst Marion Roussel (Kansas City, MO) to work on this manuscript.

REFERENCES


Copyright 2000 by Turner White Communications Inc., Wayne, PA. All rights reserved.