The Management of Patients With Heparin-Induced Thrombocytopenia Who Require Anticoagulant Therapy*

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For patients with heparin-induced thrombocytopenia (HIT), reexposure to heparin is generally not recommended. However, these patients are likely to require anticoagulation therapy at some point in the future. During acute HIT, when thrombocytopenia and anti-heparin-platelet factor 4 antibodies (or *HIT antibodies*) are present, therapy with heparin must be avoided. In patients with subacute HIT, when platelets have recovered but HIT antibodies are still present, therapy with heparin should be avoided. In patients with a remote history of HIT, when HIT antibodies have cleared, heparin reexposure may be safe, although recurrent HIT has been described in some patients. For all of these patients, the use of alternate anticoagulant agents, including direct thrombin inhibitors and anti-Xa agents, is preferable. There is an increasing amount of data supporting the use of these alternative agents in a wide variety of clinical circumstances, including thromboprophylaxis and treatment of acute thrombosis. Except for a few clinical situations, it is generally possible to avoid heparin reexposure in patients with a history of HIT.
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Abbreviations: CPB = cardiopulmonary bypass; DVT = deep venous thrombosis; ELISA = enzyme-linked immunosorbent assay; HIT = heparin-induced thrombocytopenia; IVC = interior vena cava; PCI = percutaneous coronary intervention

Heparin is administered in a wide variety of clinical situations, exposing a large number of patients to the potential development of heparin-induced thrombocytopenia (HIT). Many of these same patients will require anticoagulation therapy in the future, especially those with underlying thrombophilia or cardiovascular disease. The safety of heparin reexposure in a patient with a history of HIT is unclear. The limited data regarding reexposure to heparin focus on short-term reexposure, often for cardiovascular procedures. However, some patients will require extended treatment with an anticoagulant, as in the treatment of venous thromboembolism and unstable angina, or in extended prophylaxis for orthopedic or other major surgeries. There have been few data reported and few guidelines established for anticoagulation therapy in patients with a history of HIT.

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Selection of Alternative Anticoagulation Agents

The use of alternative anticoagulant agents for the treatment of patients with HIT is based on the premise that these agents do not generate or cross-react with anti-heparin-platelet factor 4 antibodies (or *HIT antibodies*), and are effective and safe for the prophylaxis or treatment of thrombosis. Available agents include parenteral direct thrombin inhibitors and factor Xa inhibitors.

Direct Thrombin Inhibitors

Direct thrombin inhibitors are fundamentally different from heparin in structure, do not generate or cross-react with HIT antibodies, and are approved for the treatment of acute HIT.[1,2] These agents thus represent a treatment option for patients with a history of HIT in order to avoid heparin reexposure. In some cases, this approach requires reexposure to

direct thrombin inhibitor therapy. The direct thrombin inhibitor lepirudin is a recombinant protein. Hypersensitivity reactions to lepirudin have been reported with initial exposure and reexposure, and a proportion of patients (44 to 74%) develop antibodies to lepirudin.[3] These antibodies do not interfere with the function of the drug, but in a small subset of patients may result in delayed clearance, which is associated with an increased half-life and reduced dose requirements.[4] It is not clear whether these antibodies will affect subsequent lepirudin dosing; however, and reexposure is generally well-tolerated.[5,6] Lepirudin antibodies may cross-react with bivalirudin, a synthetic hirudin analog, although the clinical significance of these antibodies is unknown.[7] Argatroban does not appear to be associated with antibody development, and reexposure is well-tolerated.[8]

Danaparoid

Danaparoid, which is composed of heparan, dermatan, and chondroitin sulfates, has been used extensively in the treatment of patients with HIT in a wide variety of clinical situations. Despite 15% *in vitro* cross-reactivity of HIT antibodies with danaparoid, it seldom causes a worsening of HIT.[9,10] Danaparoid, where available (it is unavailable in the United States), is commonly use to treat HIT patients, and there is extensive experience in both HIT and non-HIT patients.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that has been extensively studied for use in orthopedic and abdominal surgery prophylaxis, and the treatment of deep venous thrombosis (DVT) and pulmonary embolism.[11] Small studies[12,13] have demonstrated no cross-reactivity of fondaparinux with HIT antibodies by *in vitro* activation assays, but there is limited clinical experience in HIT patients. The development of HIT antibodies was observed in a small percentage of patients receiving fondaparinux for prophylaxis for orthopedic surgery, equal to the rate of antibody formation in the group receiving enoxaparin, but none of the patients in either group developed clinical HIT.[14] Given the low rate of *de novo* antibody formation and the apparent lack of cross-reactivity with HIT antibodies, fondaparinux may represent a relatively safe alternate anticoagulant agent for use in patients with a history of HIT.

The selection of an alternate anticoagulant agent should be based on demonstrated efficacy and safety (whether in HIT or non-HIT patients) for the intended use, familiarity with drug dosing, and the availability of monitoring techniques, when indicated. The clearance of these agents is affected by renal dysfunction (*eg*, lepirudin, danaparoid, fondaparinux, bivalirudin) or hepatic dysfunction (*eg*, argatroban), so baseline organ function must be assessed.[9] Most of these agents, especially when administered subcutaneously, are irreversible, so appropriate dosing and monitoring is essential.[9] As new agents become available, including oral thrombin inhibitors and factor Xa inhibitors, their applicability to the HIT population will depend on their safety, efficacy, and potential cross-reactivity with HIT antibodies.

Warfarin

Vitamin K antagonists, including warfarin, are commonly used for the long-term management of thrombotic disorders. The introduction of warfarin therapy in a patient with acute HIT should be deferred until the platelet count has recovered, in order to avoid venous limb gangrene.[9] Once the acute episode has passed, however, warfarin therapy can be used as for non-HIT patients when indicated.

Patient Classification

Patients with HIT requiring anticoagulation therapy can be divided into the following three groups: (1) those with active HIT (*ie*, thrombocytopenia and the presence of HIT antibodies); (2) those with recent or "subacute" HIT (*ie*, platelet recovery but detectable antibodies); and (3) those with a history of HIT (*ie*, antibodies no longer detectable). This characterization of patients, used by Warkentin and Greinacher[15] when discussing anticoagulation therapy for HIT patients undergoing cardiopulmonary bypass (CPB), is useful when considering an approach to broader anticoagulation issues.

Anticoagulation Therapy in Patients With Active HIT (Low Platelet Levels and Antibody Present)

For patients with active HIT, with associated thrombocytopenia and the presence of HIT antibodies, therapy with all forms of heparin should be avoided. This includes all routes of administration of heparin, including heparin flushes, regional anticoagulation therapy, and the use of heparin-coated catheters.[16] The options for anticoagulant treatment for patients with active HIT include the use of the direct thrombin inhibitors (*eg*, lepirudin or argatroban) or danaparoid and have been reviewed elsewhere.[9,10,16] For active HIT patients requiring full-dose anticoagulation therapy for preexisting venous