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## Heparin-induced thrombocytopenia, paradoxical thromboembolism, and other adverse effects of heparin-type therapy

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Heparin has been used clinically to treat venous thrombosis for more than 50 years. Although several new anticoagulant drugs are in development, heparin, including low-molecular-weight (LMW) heparin, remains the anticoagulant of choice to treat acute thrombotic events. The clinical effects of heparin and LMW heparin are meritorious, but adverse events do occur. Bleeding is heparin's primary untoward effect. Major bleeding occurs in 1% to 33% of patients who receive heparin therapy [1]. Additional important untoward effects of heparin therapy include HIT, heparin-associated osteoporosis, eosinophilia, skin reactions, allergic reactions other than thrombocytopenia, and alopecia. Other adverse events include frequent abnormalities of hepatic function tests and occasional hyperkalemia [1].

A summary of side effects of heparin are given in Box 1.

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### **Box 1. Side effects of heparin therapy**

#### *Potentially severe*

Bleeding  
 Acute heparin “anaphylaxis”  
 Heparin-induced thrombocytopenia

#### *(Generally) mild*

Heparin-associated osteoporosis  
 Skin reactions such as urticaria, erythematous papules, and skin necrosis  
 Abnormal liver function tests  
 Eosinophilia  
 Hyperkalemia  
 Hypoaldosteronism  
 Priapism  
 Alopecia

## **Heparin-induced thrombocytopenia**

### *Clinical manifestations*

Heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome (HITT) represent a disease spectrum triggered by an immune response to heparin. The diagnosis of HIT/T (HIT +/- thrombosis) depends on clinical criteria with confirmation by specific laboratory tests. Unexplained thrombocytopenia or thromboembolism in a patient receiving heparin is sufficient reason to make a presumed clinical diagnosis of HIT/T [2,3]. A link however, must be established between heparin and thrombocytopenia; other causes of thrombocytopenia must be excluded. The clinical features of immune-mediated HIT/T are summarized in Box 2.

The diagnosis of HIT should be based on clinical criteria and platelet count and not on HIT laboratory tests. The commonly accepted diagnostic criteria include:

- Thrombocytopenia: decrease of 50% or more from baseline platelet numbers (strong suspicion should occur at 30% decrease from baseline levels)
- Absence of other cause of thrombocytopenia
- Confirmation by a heparin-associated antibody assay
- Return to normal platelet numbers when heparin stopped

Most authors define thrombocytopenia in HIT as a platelet count of less than 150,000 per  $\mu\text{L}$  or a decrease in platelet count to 50% from baseline; however,

### **Box 2. Clinical features of heparin-induced thrombocytopenia type II**

Usual onset at day 3–14 (median day 6).

Nadir platelet count: usually 30,000–60,000, but may be as low as 5000. The most appropriate definition is a 50% decrease in platelet numbers from the baseline values.

Risk occurs with all methods of heparin administration. Risk occurs most commonly with continuous infusion of heparin. HIT also is seen with heparin flushes (500 U/d) and with heparin-coated catheters. Risk is higher with intravenous than subcutaneous administration. Additionally, bovine heparins may induce greater risk than porcine heparins, which induce a greater risk than LMW heparins.

Can occur within hours of heparin exposure in previously heparin-treated patients.

Increased incidence in patients with recent surgery (primarily venous problems).

Increased incidence in patients with pre-existing cardiovascular disease (primarily arterial).

Risks are equal in men and in women. Age is not a factor, and there is no relation to inherited deficiency or acquired defects of clotting factors.

HIT/T should be suspected if there is a 30% unexplained drop in the platelet count [4,5]. There is no given platelet count at which a diagnosis of HIT can be made with certainty. Thrombocytopenia may be relative but not absolute. For example, platelet counts reduced only 50% from a high normal baseline would remain normal and, therefore, would not be labeled as thrombocytopenia. HIT typically is associated with a platelet count of 38,000 to 60,000 per  $\mu\text{L}$ , with lower counts being less common. Postoperative cardiac patients represent a special group, because most patients have platelet counts between 100,000 per  $\mu\text{L}$  and 150,000 per  $\mu\text{L}$  on postoperative day one [4,5]. Although studies by the author (JMW) are in progress, preliminary data suggest that HIT may be associated with an immediate postoperative platelet count decrease of more than 50% from the preoperative count, and no, or only a slow, trend of increasing platelet count over the early postoperative days. Care must be exercised to exclude postoperative platelet consumption processes such as unrecognized hematoma formation or bleeding [4,5].

The time required to develop HIT antibody from the initial heparin exposure appears to be about 5 days but can be much longer or shorter if an anamnestic response is produced [6,7]. The dose of heparin and route of administration do not seem to make any difference in the frequency of HIT. Like other antibody responses, the HIT antibody response varies in an individual patient. This can be seen from the varying titers of antibody to the heparin-platelet factor (PF)

4 complex [8,9]. The duration of antibody production in individual patients is also variable. The antibody response, in most patients, ranges from weeks to months, but patients have remained HIT positive for more than 1 year as assessed by laboratory assay. One may observe a delay in platelet rise in some HIT patients with a negative lab assay after heparin removal; one also may see a positive laboratory assay in the face of rising platelet counts after heparin removal [2]. Both cases are HIT/T.

Failure to monitor platelet counts and to assess the patient for manifestations of thromboembolism or hemorrhage may result in a delay of diagnosis. Platelet counts should be done daily or every other day in all patients on heparin or LMW heparin therapy; this applies to any platelet counts and any route of heparin exposure [10–12]. Rechallenge with heparin after resolution of the thrombocytopenia to confirm a diagnosis of HIT/T is dangerous and should not be performed.

Heparin-induced thrombocytopenia occurs in approximately 2% to 3% of all individuals exposed to heparin [5,13]. The majority of cases are found in medically and surgically treated adults, but HIT also can be observed during pregnancy and in the newborn [14–16]. The most dramatic clinical expression of HIT is HIT antibody-driven thrombosis (HITT). Thrombosis can occur anywhere throughout the venous and arterial circulation. Thrombosis can develop when platelet counts are normal. Previous reports suggested that arterial thrombosis was more common than venous thrombosis [2]. More recent reports, however, document a higher frequency of venous thrombosis than arterial thrombosis [16,17]. HITT is associated most commonly with deep vein thrombosis and pulmonary embolism, but unusual thromboses, including mesenteric ischemia, spinal artery thrombosis, visceral infarctions, cerebral infarction, and myocardial infarction are not uncommon [4,16]. Thrombi probably also are formed in many HITT patients in locations that do not result in clinically expressed adverse events.

Data from multiple institutions suggest that the diagnosis of HIT/T predicts future clinically significant thrombotic events [2,4,16,18]. Patients with clinically diagnosed HIT have a 35% probability of developing a clinically significant thrombosis during their hospitalization [16]. Patients with HIT or HITT carry a reported mortality of 25% to 30% and amputation rates of up to 25% [16]. The apparent paradox of a fall in platelet count with thrombotic rather than hemorrhagic complications is analogous to the syndrome of thrombotic thrombocytopenic purpura [2]. These patients therefore require careful monitoring and aggressive treatment, including perhaps prophylactic anticoagulant therapy.

### *Mechanism of action*

Heparin-induced thrombocytopenia and thrombosis is an immune reaction triggered by the generation of antibodies that bind to a complex of heparin coupled with peptides, proteins, or glycoproteins on the platelet and endothelial cell surface [19–26,50]. The accepted mechanism of the pathophysiology of HIT is based on the development of an IgG antibody targeted towards the heparin-PF4 complex [19,50]. This antibody causes platelet activation, aggregation, and

subsequent platelet and endothelial cell destruction [20,22,27–29,103]. The antibody is not heparin-specific, and it has been shown to react with highly sulfated materials, including dextran sulfate, pentosan polysulfate, and endothelial heparan, but not with dextran, dermatan sulfate, or desulfated heparin [23,104].

The Fab region of the antibodies recognizes the heparin-PF4 complex, and the Fc portion of the antibody recognizes the Fc $\gamma$ RIIA receptors on the platelet [19,20,21,25,30,50]. Complexes of heparin-PF4-IgG accumulate on the platelet surface, stimulating platelets that releases PF4, creating a positive feedback cycle. Platelet activation results in granule secretion, microparticle formation, conformation changes in surface glycoproteins, and the formation of platelet aggregates. In addition, the heparan sulfate on the endothelial cell surface can bind PF4. The antibody to the heparin-PF4 complex binds to the cell-bound complex, resulting in endothelial cell damage; additional damage may occur from antibody binding to endothelial heparan and other endothelial glycosaminoglycans [22,26,27,29,103]. The damaged endothelial cells act as a starting point for the thrombotic event, potentially through exposure of tissue factor, which is enhanced by the recruitment of monocytes and further tissue factor release from these cells [105]. The release of platelet microparticles [28,31] rich in phospholipid further contributes to the platelet aggregation, endothelial cell change or damage, and thrombosis.

Platelet activation plays a central role in HIT; however, platelet activation does not occur as an isolated physiological response. Leukocyte activation, leukocyte binding to platelets, leukocyte binding to endothelial cells, and the activation of the inflammatory state also occur in the presence of heparin-dependent antibodies [27,29,32,33,106,107]

The wide spectrum of clinical manifestations described in patients who develop HIT/T may be explained by the heterogeneity of the components that comprise its mechanism. HIT antibodies are commonly of the IgG<sub>2</sub> isotype, although other isotypes and IgA and IgM antibodies also have been identified in these patients [25]. A heparin-PF4 antibody titer is not always consistent with clinical manifestations of HIT [8,9], suggesting that there are other yet unknown components or mechanisms. Functional and nonfunctional antibodies, in terms of their ability to activate platelets, have been identified in patients with HIT [35,36]. Whether these nonfunctional antibodies are clinically significant is unclear. There is evidence, however, of an increased prevalence of myocardial infarction, recurrent angina, urgent revascularization, and stroke within the year following detection of antibodies [37]. There is a range of affinities of antibodies to the heparin-PF4 complex where only the highest affinity antibodies appear to cause platelet activation as demonstrated by the Serotonin Release Assay [38,39]. Other studies also have shown that antibodies from some patients with HIT can cause platelet activation independent of heparin [35].

The platelet Fc $\gamma$ RIIA receptor genotype imparts a degree of risk on patients for developing HIT, but this does not seem to be a major factor [51]. Heparin itself is heterogeneous in amino acid and protein content, and degree of sulfation from lot-to-lot and from manufacturer-to-manufacturer. These add yet other levels of heterogeneity to the spectrum of HIT.

### *Low–molecular-weight heparins*

Postulated to be less antigenic than heparin because of their smaller size, LMW heparins were thought to have a role as alternative anticoagulants in patients with HIT. From the data gathered in clinical trials throughout the 1990s, it appears that most LMW heparins are less likely than unfractionated heparin (UFH) to cause HIT/T. There appears to be a lower risk of immune sensitization and lower risk of developing HIT with LMW heparin treatment [108]. The molecular weight of heparin may contribute to its ability to generate functional antibodies. Fractions of heparin with a molecular weight of less than 5000 d do not activate platelets in the presence of antibody [41]. This may be a key factor in the lower incidence of HIT in patients treated with LMW heparin; however, data for all LMW heparins and for prophylactic and therapeutic doses are not available.

It is clear, nevertheless, that in a patient with established HIT, the use of most LMW heparins very likely would be associated with a high risk of continuation of the disease process. In vitro results unequivocally demonstrate that LMW heparins will produce platelet aggregation in the presence of heparin antibody [23,34,104]. Although the response is less than that for heparin (80% versus 100% positive reactors), it remains significant. There have been limited reports on the successful use of LMW heparin in patients with HIT [43,44,46]. Certain authors caution, however, that evidence for reducing the thrombus extension was not documented in all patients [44,45,109], and if in vitro platelet aggregation with LMW heparin is positive, treatment must be avoided or stopped [46]. The American College of Chest Physicians (ACCP) recommends that LMW heparin should not be given to patients with HIT, as the potential for cross-reactivity with the heparin antibody is high [12].

### *Laboratory assays*

There is no highly sensitive and specific laboratory test for HIT [8,9,47]. The platelet aggregation assay for confirming the diagnosis of HIT has been the clinically accepted method throughout the world for years, yet it has limitations. A mixture of reactive, normal donor platelets, patient serum, and heparin is evaluated for platelet aggregation. Modifications of this assay include the use of patient platelets in place of normal platelets [48,49] or the use of a lumiaggregometer [15] to simultaneously measure platelet activation with platelet aggregation. Clinical laboratorians have instituted specific protocols to maintain the assay sensitivity and to reduce false negative or positive responses.

The serotonin release assay (SRA) measures platelet activation caused by patient serum and heparin. Activation is determined by the release of radiolabeled serotonin from washed normal donor platelets (selected for known reactivity in the SRA) previously incubated with the labeled serotonin. The platelet aggregation assay has a high false negative rate; assay sensitivity is about 40% on average (up to 80% under optimum conditions). The SRA has a higher sensitivity of 60% to 80% [9,24]. Both assays are characterized by technical difficulties that

require expert laboratory personnel. The SRA additionally requires radiation handling, which some laboratories are not licensed or equipped for. False positives also can be obtained in the aggregation or the SRA, although they are far less common than false negatives [8,9,103].

There are two ELISA assays for quantitating antibodies to the heparin-PF4 complex (Diagnostica Stago, Asnieres, France, and GTI, Brookfield, WI, USA). Heparin or LMW heparin treatment alone provokes antibody production, which is not necessarily accompanied by thrombocytopenia [8,36], and patients clinically positive for HIT do not always have positive heparin-PF4 antibody titers [8,9].

New assays for HIT/T require clinical validation, and results of any of the current HIT/T assays should be assessed cautiously. Patients who are clinically positive for HIT may have negative responses in any one of the assays. Also, a positive response in one assay does not guarantee a positive response in the other assays. The laboratory diagnosis of HIT has not been optimized, probably because the understanding of the pathophysiological mechanisms is only beginning to be appreciated. At present, clinical observations are of foremost importance in diagnosing HIT. No laboratory diagnostic assay provides a high enough sensitivity or specificity.

### *Clinical management*

For the clinical management of patients suspected of having HIT, a meticulous search for heparin is critical, remembering that often unrecognized sources of heparin include vascular line flushes and heparin-coated catheters. All heparin should be discontinued immediately.

If the decrease in platelet count immediately after heparin administration is only moderate (10% to 20% short-term decrease from baseline), a transient HIT (type I) that is not immune-mediated should be suspected (Box 3) [2]. Laboratory

#### **Box 3. Heparin-induced thrombocytopenia type I (nonimmune, nonidiosyncratic)**

Episode of thrombocytopenia occurs early in exposure, generally in the first few days in naïve patients and in the first few hours in previously exposed patients.

Mild thrombocytopenia: 10% to 30% decrease in platelet numbers.

Clinical manifestations: none.

Mechanism: heparin-induced platelet aggregation.

True incidence: uncertain but common.

Biologic issues: episode transient. Counts normalize even with continued therapy.

Therapy: none.

Relationship to HIT II: unclear but probably none.

testing is an important consideration in such patients. This benign form of HIT would be supported by negative laboratory tests. Patients with this benign form of HIT can continue with heparin treatment without consequence.

Despite the devastating consequences of the heparin antibody, the diagnosis of the immune form of HIT is not made promptly in many hospital units. The average time from a 50% reduction in platelet count to recognition and discontinuation of heparin is 4 days [16]. Intense education of nursing staff, ancillary staff, house staff, and attending physicians can reduce time to recognition of the syndrome to less than 1 to 2 days. Educational efforts should be directed at areas in the hospital associated with frequent heparin use, such as cardiovascular surgery units, coronary care units, orthopedic units, and intensive care units. In addition, outpatients can develop thrombocytopenia, recover, and develop a thrombosis in the home setting, which would leave the diagnosis of HIT completely unsuspected [3,4].

The high probability of thrombosis in the HIT patient should prompt immediate thorough assessment for potential occlusive disease [4]. All clinical symptoms or physical signs should be evaluated with appropriate diagnostic testing. Local swelling, erythema or pain, and blue digits require Doppler testing or venography. Dyspnea should prompt ventilation perfusion (V/Q) scanning. Subtle neurologic symptoms should prompt cerebral angiography or magnetic resonance angiography (MRA). A commonly overlooked syndrome in these patients is mesenteric ischemia. Patients with unexplained acidosis and elevated leukocyte counts should undergo mesenteric angiography, MRA, or diagnostic laparotomy or laparoscopy. Postoperative coronary artery bypass patients have a high frequency of venous graft closure [16]. Coronary angiography with consideration of percutaneous transluminal coronary angioplasty (PTCA) using alternative anticoagulants should be considered in these patients.

Early discontinuation of heparin alone does not appear to affect the thrombotic event rate significantly, although early recognition may improve mortality [16]. In one study, one third of all HIT patients in whom heparin was stopped as soon as the diagnosis was made developed a new thrombosis [16]. Thus, prophylaxis against thrombosis may be beneficial. Although the discontinuation of heparin removes the stimulus for HIT antibody production, it also eliminates the usual treatment for thrombosis. Untreated thrombus will continue to propagate and become a clinically significant thrombotic event.

#### *Direct thrombin inhibitors*

The recommended treatment for patients with HIT antibody is to anticoagulate with a direct thrombin inhibitor [12]. Specific treatment measures are as follows:

1. Stop heparin immediately.
2. Alternate rapid-onset antithrombotic therapy if original condition persists
  - a. Lepirudin at 0.4 mg per kg bolus followed by 0.15 mg per kg per hour infusion.

- b. Argatroban at 2 mg per kg per min infusion (not to exceed 10 mg per kg per min) to obtain an aPIT 1.5 to 3.0 times baseline (not to exceed 100 seconds).
3. Assess immediately for evidence of occult thrombosis; rapid-onset antithrombotic if suspected or found.
4. If prophylaxis is needed, argatroban may be used as described above.

The FDA has approved hirudin (lepirudin, Refludan<sup>®</sup> [Berlex, Wayne, NJ]) and argatroban (Argatroban<sup>®</sup> [GlaxoSmithKline; Philadelphia, PA]) for treating HIT-associated thrombosis. Argatroban also has been approved for prophylaxis of HIT-associated thrombosis. These drugs have no structural similarity to heparin and, therefore, do not cross-react with the HIT antibody [4,52,72,104]. The level of anticoagulation can be monitored with standard activated partial thromboplastin time (aPTT) testing for both drugs.

A multi-center study conducted to evaluate the safety and efficacy of argatroban in patients with HIT used continuous intravenous argatroban at 2 µg per kg per minute on average for approximately 6 days (14 days maximum) in 160 HIT patients and 144 patients with HITT [53]. Dosage was adjusted to maintain the aPTT between 1.5 times to 3.0 times baseline. Outcomes assessed during therapy and for 30 days following therapy were compared with those from 147 HIT and 46 HITT historical control patients.

The primary efficacy composite endpoints of new thrombosis, all-cause amputation, or all-cause death were reduced significantly in argatroban-treated patients versus controls with HIT (25.6% versus 38.8%,  $P = 0.014$ ). In patients with HITT, the composite incidence in argatroban-treated patients was 43.8% versus 56.5% ( $P = 0.13$ ). Significant between group differences by time-to-event analysis of the composite endpoint favored argatroban treatment in HIT ( $P = 0.01$ ) and HITT ( $P = 0.014$ ) patients. Argatroban therapy, relative to controls, also significantly reduced new thrombosis and death caused by thrombosis ( $P < 0.05$ ).

No difference was detected in the incidence of major bleeding (HIT: 3.1% versus 8.2%,  $P = 0.078$ ; HITT: 11.1% versus 2.2%,  $P = 0.077$ ). Minor bleeding was similar in both groups (HIT: 40% versus 41%; HITT: 42% versus 41%,  $P < 0.001$ ), primarily at procedural sites. Argatroban-treated patients achieved therapeutic aPTTs generally within 4 to 5 hours of starting therapy, and compared with controls had a significantly more rapid rise in platelet count ( $P = 0.0001$ ).

Lepirudin was evaluated for safety and efficacy in a multicenter study in patients with confirmed HIT administered by one of four intravenous regimens: A1, HITT patients ( $n = 51$ ), 0.4 mg per kg bolus followed by 0.15 mg per kg per hour; A2, HITT patients receiving thrombolysis ( $n = 5$ ), 0.2 mg/kg bolus followed by 0.1 mg/kg per hour; B, HIT patients ( $n = 18$ ), 0.1 mg per kg per hour; C, during cardiopulmonary bypass surgery ( $n = 8$ ), 0.25 mg per kg bolus and 5 mg boluses as needed [54]. Outcomes of 71 patients were compared with a historical control group of 120 patients. The incidence of the combined endpoint (death, amputation, and new thromboembolic complications) was reduced

significantly in lepirudin-treated patients ( $P = 0.014$ ). Platelet counts increased rapidly in 88.7% of treated patients. Bleeding rates were similar in both groups.

In a second study of lepirudin, patients with confirmed HIT received treatment by one of three dosing regimens for 2 to 10 days or longer: A1, treatment, 0.4 mg per kg bolus followed by 0.15 mg per kg per hour ( $n = 65$ ); A2, in conjunction with thrombolytic therapy, 0.2 mg per kg followed by 0.1 mg per kg per hour ( $n = 4$ ); B, prophylaxis, 0.01 mg per kg per hour ( $n = 43$ ) [55]. Outcomes of 95 patients compared with those of 120 historical control patients showed aPTT less than 1.5 times baseline and platelet count normalization by day 10 in 69% of treated patients. Within 35 days after HIT confirmation, fewer lepirudin-treated patients than historical controls experienced adverse outcome events ( $P = 0.12$ ). Bleeding events in the lepirudin group were more frequent (44.6% versus 27.2%;  $P = 0.0001$ ).

These studies showed that anticoagulation with argatroban or hirudin significantly reduced the risk of thrombosis and thromboembolic complications (new thrombosis, amputation, and death) associated with HIT. This benefit was achieved with an acceptable safety profile.

Hirudin is pharmacologically distinct from argatroban and exhibits a different safety and efficacy profile [56]. Argatroban has a rapid onset of action and is dissociated rapidly from thrombin following discontinuation (ie, reversible). Its half-life is approximately 40 minutes. Hirudin has a slow dissociation from thrombin and a longer half-life of approximately 80 minutes. Hirudin is a protein and can generate antibodies that increase its anticoagulant activity by prolonging the half-life or antibodies that decrease its anticoagulant effect [57]. Argatroban does not induce antibody generation [110]. Argatroban is cleared through the liver; hirudin is cleared through the kidney.

Because patients with HIT have an extremely high risk of developing thrombosis, treatment of thrombosis is essential [3–5,40]. Prophylaxis against thrombosis also should be considered [3–5,40]. For documented clinical thrombosis associated with HIT, patients should be treated with a direct thrombin inhibitor at therapeutic aPTT levels for 7 to 10 days. Conversion to warfarin can be done where appropriate with the precautions described subsequently. For prophylactic treatment of patients with HIT despite no other indication for anticoagulation, a direct thrombin inhibitor can be initiated with low levels of anticoagulation until the thrombocytopenia resolves. This regimen should be continued until laboratory evidence is provided that the HIT antibody is not detected.

### *Warfarin*

For patients with mechanical prosthetic valves, atrial fibrillation, and an underlying hypercoagulable state, the ideal management strategy would be to initiate oral anticoagulation while maintaining a therapeutic level of anticoagulation with an intravenous thrombin inhibitor [3–5,40]. To avoid skin necrosis, full anticoagulation with warfarin can be achieved once platelet counts exceed 100,000 per  $\mu\text{L}$  [58]. Once the international normalization ratio (INR) for warfarin is stable in the therapeutic range, the intravenous thrombin inhibitor

can be tapered off and then discontinued. Low-dose aspirin can be added to the regimen once warfarin is therapeutic.

### *Plasmapheresis*

In severe cases, or for example when patients require emergency cardiac surgery where they will be exposed to heparin, plasmapheresis can be performed to reduce the titer of heparin antibody [3–5,40]. There is improved survival of patients treated with early plasmapheresis compared with historic controls not treated with plasmapheresis [59,60,71]. Plasmapheresis is performed daily until a negative HIT antibody test is obtained. Patients who remain HIT antibody positive after three consecutive plasmapheresis treatments can be given immunoglobulin therapy. It is important to recognize that patients who are treated with plasmapheresis will have mechanical depletion of their clotting factors. Therefore, during plasmapheresis, only small doses of warfarin or other anticoagulants should be administered.

### *Thrombolytic agents*

Patients who have limb-threatening or life-threatening thrombosis that is not corrected with thrombin inhibitor treatment can be treated with selective thrombolytic infusion [3,4]. Lower doses for postoperative patients (urokinase 30,000–60,000 U/hour) and higher doses (urokinase 50,000–200,000 U/hour) for nonpostoperative patients are recommended [3,4,61–63]. Fibrinogen levels are monitored every 8 hours to maintain levels at 200 mg per dL. Thrombolytic infusions are discontinued or decreased if significant clinical bleeding is observed and are continued until angiographic or other objective imaging evidence of complete resolution of thrombus is found. Selective thrombolytic infusion has been more successful than surgical thrombectomy. The endothelial damage that occurs with thrombectomy, combined with the involvement of endothelial cells observed with HIT antibody, may explain the limited success with thrombectomy. Surgical thrombectomy remains a reasonable therapy, however, in patients who have dire clinical circumstances and cannot afford the time required for selective thrombolytic infusions.

### *Other anticoagulation needs in the heparin-induced thrombocytopenia patient*

Heparin-induced thrombocytopenia patients, in addition to needing anticoagulation to treat thrombosis, can require anticoagulation for non-HIT related events such as treatment of myocardial infarction and unstable angina. A second group is those patients requiring long-term anticoagulation such as for heart valves or atrial fibrillation. For these situations, the use of a direct thrombin inhibitor if immediate anticoagulation is needed with a switch over to warfarin is probably the best option. Optimum dosing regimens have not been established in all cases, however.

Perhaps the greatest obstacle to overcome in the management of patients with HIT antibody is treatment of those patients who require coronary revascularization or cardiac surgery. These patients require anticoagulation to successfully perform percutaneous coronary interventions, coronary bypass surgery, or cardiac

valve surgery. Standard heparin protocols, restricted to the operative period, can be employed after antibody titers are allowed to decrease [2,65]. Heparin postoperatively or for long-term use should be replaced with a direct thrombin inhibitor or warfarin.

### *Additional management options*

Most of the early anticoagulation treatment alternatives for patients with HIT have been less than optimal because of high bleeding risk, slow onset of activity, long half-life, poor efficacy, and lack of an antidote.

### *Traditional treatment options*

The conventional anticoagulants aspirin, dextran, and warfarin are of limited value in the treatment of patients with HIT-associated thrombosis [4]. Dextran interferes with platelet aggregation and fibrin polymerization, thus delaying the onset of aggregation and the overall degree of aggregation. Tachyphylaxis or anaphylaxis to dextran can be seen, however. Aspirin has been used with some success but often does not have an effect in patients with HIT [66,72]. Aspirin usually is started only after thrombocytopenia has resolved to a level of at least 100,000 platelets per  $\mu\text{L}$  whole blood. Iloprost, a prostacyclin analogue, inhibits platelet aggregation and has been used in a limited number of cardiac surgery cases with success [67].

With warfarin, the required loading period of 48 to 72 hours leaves patients without anticoagulant protection during that period. Warfarin also inhibits protein C, potentially resulting in a prothrombotic state that can lead to tissue necrosis. Warfarin should not be used as the sole treatment for HIT-associated thrombosis.

### *Danaparoid*

The low molecular weight heparinoid, danaparoid (Orgaran<sup>®</sup>; Organon, Oss, The Netherlands), is a mixture of nonheparin polysulfated glycosaminoglycans (heparan sulfate, dermatan sulfate, chondroitin sulfate, and LMW heparin). Although related to heparin in structure, danaparoid differs from heparin in degree of sulfation and molecular weight. In vitro studies using HIT-positive sera have shown a decreased incidence of platelet aggregation to danaparoid compared with heparin (eg, 18% positive reactors versus 100% for heparin) [68,104]. Although useful in many situations, treatment failures have been reported [69].

Danaparoid has been used with success in patients with HIT in several clinical situations such as hemodialysis, plasmapheresis, treatment of pulmonary emboli, treatment of venous or arterial thrombosis, unstable angina, and during therapy with the intra-aortic balloon pump [49,70]. Because dosing guidelines are not well established, there is no antagonist to reverse this agent, and monitoring assays are not commonly available, danaparoid is not always the first drug of choice for treatment of patients with HIT. In addition, because it has a long half-

life, significant postoperative bleeding occurs. As of 2003, danaparoid will no longer be available in the United States.

#### *Ancrod*

The defibrinating agent, ancrod (Arvin<sup>®</sup>; Knoll, Whippany, NJ) is not recommended for use in patients with HIT, because it possesses an inherent risk of bleeding, thrombosis, and treatment failure [64].

#### *Future anticoagulants*

##### *Hirulog*

Hirulog (bivalirudin; Angiomax<sup>®</sup>, The Medicines Company, Parsippany, NJ) is a synthetic, direct thrombin inhibitor with a lower molecular weight than hirudin. Its structure is based on two small peptide sequences that bind directly to the active site of thrombin and to the exosite of thrombin. It is a reversible inhibitor of thrombin. It can be used in renal and hepatic-impaired patients. It is approved for anticoagulation in patients with unstable angina undergoing PTCA. It is in development for use in patients with HIT as an anticoagulant.

##### *Factor Xa inhibitors*

Anticoagulants based on the inhibition of factor Xa are another focus of new drug development. The synthetic heparin pentasaccharide Arixtra<sup>®</sup>, (Sanofi-Synthélabo Organon, Paris, France) is one example. Factor Xa inhibitors have shown no platelet aggregation response at any concentration against numerous HIT-positive sera evaluated [104]. These agents would not be expected to produce a platelet activation/aggregation response to the known HIT antibody, since they do not interact with PF4 or release PF4 from activated platelets as does heparin. It is not known, however, if these drugs are potent enough to counteract the high level of thrombin generation that produces the hypercoagulable state associated with HIT.

##### *Antiplatelet agents*

Despite the potent anticoagulant effect of direct thrombin inhibitors demonstrated in clinical trials, there remains an unacceptable level of thrombosis-related morbidity and mortality in patients with HIT. The glycoprotein (GP) IIb/IIIa platelet receptor inhibitors (abciximab, ReoPro<sup>®</sup>; Lilly, Indianapolis IN; eptifibatide, Integrilin<sup>®</sup>; COR Therapeutics, South San Francisco, CA; tirofiban, Aggrastat<sup>®</sup>; Merck, West Point, PA) and the ADP platelet receptor inhibitor (clopidogrel, Plavix<sup>®</sup>; Sanofi, Paris, France) have been shown to inhibit in vitro platelet activation and aggregation responses induced by HIT serum and heparin [28,72]. This includes inhibition of the formation of platelet microparticles. The thrombin inhibitors were not effective in suppressing this platelet activation.

Limited clinical experience suggests that GPIIb/IIIa inhibitors are effective at reducing thrombus that is resistant to thrombin inhibitor treatment [72]. In these

patients, a standard dose of a GPIIb/IIIa inhibitor was administered with a reduced dose of the direct thrombin inhibitor. There was no overt bleeding that required intervention, and all patients exhibited clinical improvement or full recovery. Although promising, optimal dosing regimens have not been established.

### **Additional side effects of heparin and low–molecular-weight heparin therapy**

#### *Bleeding*

The most common and more regularly anticipated complication of heparin therapy is bleeding [73–79]. The true incidence of major bleeding has been sought, but is only an estimate commonly ranging between 6% and 14% [73,74]. Hirsch et al have emphasized important variables relative to heparin related bleeding [11,73]. These are the dose of heparin administered, the method of administration (ie, continuous versus intermittent), and the comorbid and concomitant therapy administered. Thus, heparin therapy is associated more commonly with bleeding when given to chronic alcoholics [78]. More complex and not completely resolved is the consideration that bleeding is seen more commonly in patients on aspirin [73,78,79]. Because this is an not uncommon treatment combination in patients with arterial vascular disease, clinical vigilance for bleeding is the only intelligent approach.

A recent MedWatch FDA alert pointed out that excessive bleeding was noted in individuals at least 65 years of age when given enoxaparin, and the bleeding risk increased after age 65. This MedWatch FDA alert was limited only to enoxaparin and did not involve other FDA-approved LMW heparins [80].

#### **Acute heparin reaction (anaphylaxis)**

A rare, but potentially lethal acute reaction to heparin can occur. The event is abrupt and clinically dramatic [81]. It has been seen only in patients previously treated with heparin. It merits emphasis that the heparin exposure need not be a quantitative one, since it has occurred with heparin exposure as minimal as heparin flush or use of a heparin coated catheter. Symptoms occur dramatically within 5 to 10 minutes of institution of the heparin bolus and include abrupt onset of chills and fever, tachycardia, diaphoresis, and nausea. Hypotension may be noted, although most patients have become abruptly and transiently hypertensive. One of the authors (RLB) has noted three cases of anaphylaxis at initial exposure (first or second dose) to enoxaparin; these generally were associated with urticaria, wheezing, respiratory distress, and hypotension. These individuals were treated later with other heparins or LMW heparins without adverse sequelae. These cases are on file with the FDA. Retrosternal chest pain with the pattern of an acute myocardial infarction is common. Finally, a global amnesia syndrome has been

linked to the crisis event. This anaphylaxis-like reaction has all of the features of an IgE-stimulated response. Immediate cessation of the heparin is critical. Other nonheparin antithrombotic agents should be used to treat the patient.

### **Heparin-associated osteoporosis**

Prolonged heparin exposure has been correlated with the development of osteoporosis [82,83]. The clinical findings that led to the evaluation of this finding were the unexpected development of bone pain or the identification of vertebral body, rib, or other fractures. The clinical correlate was that patients had been on long-term heparin (in excess of 6 months) and usually at daily doses in excess of 15,000 anti-Xa units [11]. Limited epidemiological and controlled studies are available to define the incidence of heparin-associated osteoporosis. In addition, many of the studies have focused on pregnant patients, since such patients represent a group likely to have a long duration of therapy. Because pregnancy itself is commonly associated with osteoporosis, however, such data must be cautiously interpreted. In randomized trials, Howell et al identified a 5% incidence of vertebral fractures in women treated during pregnancy with FU heparin [84]. Monreal, in a randomized study of 40 men and 40 women (mean age of 68) on long-term heparin therapy, identified a 10% incidence of vertebral fractures [85]. Six of the seven occurred with FU heparin, the seventh with LMW heparin (fragmin). This study found that there was no difference in bone density between the group developing fractures compared with those without fractures. The researchers could not show a correlation between the lumbar bone density and the dose or duration of therapy [85].

Barbour et al evaluated the subclinical occurrence of heparin-associated osteoporosis in pregnancy by means of bone densitometry in a prospective, consecutive cohort of 14 pregnant women requiring heparin therapy and 14 pregnant controls matched for age, race, and smoking status [86]. Proximal femur bone density measurements were taken at baseline, immediately postpartum, and 6 months postpartum in the cases and controls. Vertebral measurements also were obtained on both groups immediately postpartum and 6 months postpartum. Bone density relative to heparin dose and duration was examined. Five of 14 cases (36%) had a 10% decrease from their baseline proximal femur measurements to their immediate postpartum values, whereas none occurred in the 14 matched controls ( $P = 0.04$ ). Mean proximal femur bone density measurements also decreased, and this difference was still statistically significant 6 months postpartum ( $P = 0.03$ ). This study concluded that no clear dose-response relationship could be demonstrated and that FU heparin adversely affected bone density in about 33% of exposed patients [86].

Dahlman studied the effect of long-term heparin treatment during pregnancy and the incidence of osteoporotic fractures and thromboembolic recurrence [87]. Long-term subcutaneous prophylaxis with heparin twice daily in pregnancy was used in 184 individuals. The dose of heparin was adjusted to antifactor Xa

activity or activated partial thromboplastin time and different regimens were given depending upon risk stratification. Symptomatic osteoporotic fractures of the spine occurred postpartum in four women (2.2%). The mean dosage of heparin ranged from 15,000 to 30,000 IU per 24 hours (mean 24,500 IU per 24 hours), and the duration of treatment was from 7 to 27 weeks (mean 17 weeks). Despite prophylaxis with heparin, thromboembolic complications occurred in five women. Thus, osteoporotic vertebral fractures were found in 2.2%, and these correlated with the amount of heparin administered. There were no thromboembolic events, thrombocytopenias, or excessive hemorrhage. Hunt et al, during a study of LMW heparin (fragmin) for thromboprophylaxis in 34 high-risk pregnancies identified one woman who developed an osteoporotic vertebral collapse postpartum [88]. This woman had no other risk factors for osteoporosis. Parenthetically, this study supported the efficacy of LMW heparin in preventing recurrent thromboembolic disease in pregnant women at high risk. In this study, the incidence of osteoporotic fracture was 3%; however, bone density studies, to assess asymptomatic osteoporosis, were not reported.

In a prospective matched cohort, Douketis et al studied the effects of long-term (> 1 month) FU heparin therapy on lumbar spine bone density [89]. Twenty-five women who received heparin during pregnancy and 25 matched controls underwent dual photon absorptiometry of the lumbar spine in the postpartum period. None of 25 heparin-treated patients developed fractures. Heparin-treated patients had a 0.082 g per cm<sup>2</sup> lower bone density compared with untreated controls, which was statistically significant ( $P = 0.0077$ ). There were six matched pairs in which only the heparin-treated patient had a bone density below 1.0 g per cm<sup>2</sup>, compared with only one pair in which only the control patient had a bone density below this level ( $P = 0.089$ ). The duration of heparin therapy, the mean daily dose, and the total dose of heparin were not at levels of independent significance. They concluded that long-term heparin therapy was associated with a significant reduction in bone density, although fractures were uncommon. They could not show a correlation between the lumbar bone density and the dose or duration of heparin therapy. This is in contradistinction to the generally held views that heparin-induced osteoporosis is related to the dose and duration of therapy. A variety of studies have focused on the mechanism whereby heparin affects bone metabolism and structure. Muir et al treated rats with once-daily subcutaneous injections of FU heparin or saline for 8 to 32 days and monitored the effects on bone histomorphometrically and measured urinary type 1 collagen cross-linked pyridinoline (PYD) and serum alkaline phosphatase as surrogate markers of bone resorption and formation [42]. Biochemical markers of bone turnover showed that heparin produced a dose-dependent decrease in serum alkaline phosphatase and a transient increase in urinary PYD, thus confirming the histomorphometric data. It was concluded that heparin decreases trabecular bone volume by decreasing the rate of bone formation and increasing the rate of bone resorption [42]. In a subsequent study, this group evaluated the effect of LMW heparin in a similar model system [90]. It was found that FU and LMW heparin decreased cancellous bone volume in a dose-dependent fashion but caused significantly more bone loss

than did LMW heparin. The biochemical markers of bone turnover demonstrated that both heparins produced a dose-dependent decrease in serum alkaline phosphatase, consistent with reduced bone formation, whereas, only the FU heparin caused an increase in urinary PYD, consistent with increased bone resorption. Researchers concluded that FU heparin decreases cancerous bone volume by decreasing the rate of bone formation and increasing the rate of bone resorption. In contrast, LMW heparin causes less osteopenia, because it only decreases the rate of bone formation [90].

Panagakos demonstrated that heparin induces osteoporosis by enhancing the effects of other bone resorbing factors, particularly parathyroid hormone [91]. Shaughnessy further examined the issue of calcium loss by an *in vitro* calcium release assay and demonstrated that size and sulfation of the heparins were the major determinants of the promotion of bone resorption [92]. Shaughnessy's extrapolation was that LMW heparin preparations would, therefore, reduce the risk of the expected heparin-associated osteoporosis.

Murray et al examined bone density in a rabbit model [93]. A reduction in cortical and trabecular bone density was seen with FU heparin ( $P < 0.05$ ) and high molecular weight heparin ( $P < 0.01$ ) but not with LMW heparin.

Thus, heparin-associated osteoporosis is a clinically uncommon event occurring in less than 5% of long-term heparin-treated patients. The evidence supports a lesser risk with LMW heparin than with FU heparin. The mechanisms appear to be related to impaired bone deposition and formation plus enhanced bone resorption with FU heparin. A change in new bone deposition appears to be the major mechanism with LMW heparin. Most clinical evidence supports the view that long-term therapy (ie, > 6 months) and a higher dose increases the risk of bone changes.

From these observations, the authors recommend that bone density studies be done in patients whose duration of therapy will be greater than 6 months at an equivalent of 20,000 anti-Xa U per day, or at 3 months if the dose will exceed 20,000 anti-X U per day. In addition, they encourage calcium supplements. If the patient is going to be on low-dose subcutaneous FU or LMW heparin for 1 year or more, baseline bone density studies are recommended, and repeat comparative studies should be done yearly. If a significant change occurs, and continued heparin is required, alendronate should be started [10].

### **Heparin-related skin reactions**

Three general types of skin reactions can occur with heparin therapy [5,40,94]. The most common are those seen in patients being treated with subcutaneous heparin. These are small ecchymotic or erythematous papular or nodular lesions that are slightly tender and in general less than  $1 \times 1$  cm in size. These occur at the sites of injection. Although at times these are the result of violated sterile technique and therefore, represent infections, most are sterile and require no change in therapy except the selection of an alternate site. The exact mechanism is not certain, but local cytokine release is the working concept.

A second skin reaction is that of urticarial, often pruritic, lesions, again largely at the sites of subcutaneous injection. These allergic reactions commonly have been associated with the vehicle for the heparin and often can be avoided by either a change in the brand of heparin or the use of an antihistamine or ice at the injection site at the time of the injections.

Heparin-induced skin necrosis is the most serious form of dermal reaction and fortunately the least common [94–98]. These lesions have many features similar to Coumadin necrosis, but the pathophysiology is distinctly different. The route and form of heparin is unrelated to this occurrence. Commonly, these begin 5 to 10 days into the heparin therapy and are manifested on the extremities, abdominal wall, or nose. Several of the case reports highlight their occurrence on the dorsum of the hand [95,97]. The onset is abrupt, with a dusky or erythematous plaque-like lesion that can evolve rapidly into a hemorrhagic bullae with necrosis. The exact pathophysiologic basis for these necrotic lesions is not clear. The antibodies found in heparin-induced thrombocytopenia have been seen in many of the patients in whom it has been sought, yet only about 25% of them will develop HIT II. These lesions signal an acute need to discontinue the heparin therapy and select an appropriate alternative agent.

### **Altered liver function tests**

Abnormal liver function studies, primarily a transaminasemia of minimal degree, have been correlated with long-term heparin administration. The finding is uncommon, only 5% to 10% of patients, and the pathophysiologic mechanisms have never been defined. These changes revert to normal when the heparin is discontinued and are, thus far, thought to be without clinical significance [5,40].

### **Heparin and eosinophilia**

Eosinophilia occurs in 5 to 10% of patients receiving FU or LMW heparin therapy [5,40,99]. The eosinophilia is asymptomatic. In almost all of the patients it is unrelated to systemic allergic reactions, dermal allergic reactions, skin necrosis, or any other evident symptom complex. It is not associated with any physiologic changes or sequelae. The eosinophilia abates 4 to 8 weeks after cessation of heparin therapy. The current hypothesis relative to this occurrence is the activation of CD4 cells with the subsequent release of GM-CSF, interleukin-3 (IL-3) and IL-5, which can induce eosinophilia [5].

### **Hyperkalemia hypoaldosteronism and related metabolic abnormalities**

Prolonged heparin therapy has been recognized to be associated with functional hypoaldosteronism, hyperkalemia, and correlate metabolic abnormalities [11,100,101]. Although rare, the evidence supports heparin suppression of

synthesis of aldosterone [100]. Cessation of the heparin results in resolution of the metabolic abnormalities.

### **Priapism**

Priapism has been considered to be a possible complication of heparin therapy [11]. In the few reports available, it is not clear whether specificity of a vascular occlusive event is present or whether this simply represents thrombosis as part of a HIT II event. The authors favor this latter pathophysiologic explanation.

### **Alopecia**

Alopecia has been related to long-term heparin therapy [5,11,40]. Neither its occurrence nor potential pathophysiologic mechanisms have been defined well.

### **Recent new precautions and adverse reaction reports**

In January, 2002 [102], the FDA released a MedWatch report regarding warnings of enoxaparin use in patients with prosthetic heart valves. The FDA report suggested that Lovenox (enoxaparin) Injection not be used for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were in pregnant women in whom thrombosis led to maternal and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism [102].

The same report noted potential problems in pregnancy. Concerning teratogenicity, there have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defects [102]. Nonteratogenicity problems reported included postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anticoagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother or fetus. Pregnant women receiving enoxaparin should be monitored carefully. Pregnant women and women of child-bearing age should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy [102]. In addition, this MedWatch report alerted clinicians to the fact that about 80 cases of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal or epidural anesthesia or spinal puncture have been reported. Thus far, these MedWatch reports appear to be limited to enoxaparin. Clinicians using antithrombotics are encouraged to check the FDA MedWatch reports frequently for similar information.

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