Heparin is commonly used to prevent thrombosis in patients undergoing surgery and in nonambulatory patients in critical care units. Heparin-induced thrombocytopenia (HIT) is a rare and serious complication associated with the use of heparin.1-3 HIT can be divided into 2 clinically separate types (Table 1). Type I (HIT-I) occurs in 10% to 20% of patients receiving heparin and typically is manifested by a mild reduction in the platelet count 1 to 4 days after initiation of heparin therapy. The underlying cause of HIT-I remains unknown but is believed to involve a direct reaction of heparin with platelets that leads to platelet clumping.1-3 HIT-I is benign and usually resolves without further sequelae after heparin therapy is discontinued.1,3 Type II (HIT-II) occurs in 1% to 3% of patients after receiving heparin for 5 to 14 days.1,3 HIT-II is an immune-mediated reaction that involves the binding of heparin to platelet factor 4 (PF4), a heparin-binding protein found on platelet surfaces.1-4 The heparin-PF4 complex then reacts with immunoglobulin G (IgG), resulting in endothelial injury and platelet activation.5 This sequence of events can lead to a 30% to 50% decrease in platelet counts, usually to less than $100 \times 10^9/L$ (normal range $150-450 \times 10^9/L$). Because of platelet activation, the pathological cascade of HIT-II can lead to thromboembolism.2-4 The hypercoagulable nature of HIT-II makes it a more serious condition than HIT-I.2-3 Thrombosis, which increases the risk of morbidity and mortality, develops in approximately 30% to 80% of patients with HIT-II.3 Thrombosis can

Table 1 Clinical comparison of heparin-induced thrombocytopenia type 1 (HIT-I) and type 2 (HIT-II)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIT-I</th>
<th>HIT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset after initiation of heparin therapy</td>
<td>1-4 days</td>
<td>5-14 days</td>
</tr>
<tr>
<td>Typical platelet count</td>
<td>Mild decrease from baseline; usually $&lt;150 \times 10^9/L$, rarely $&lt;100 \times 10^9/L$</td>
<td>$30%-50%$ decrease from baseline or $&lt;150 \times 10^9/L$, typically $&lt;100 \times 10^9/L$</td>
</tr>
<tr>
<td>Incidence</td>
<td>10%-20% of patients receiving heparin</td>
<td>1%-3% of patients receiving heparin</td>
</tr>
<tr>
<td>Etiology</td>
<td>Unknown</td>
<td>Immune-mediated</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Benign; typically resolves upon discontinuation of heparin</td>
<td>Thrombosis develops in 50%; increased risk of morbidity and mortality from stroke, limb amputation, pulmonary embolism, and stroke without therapeutic intervention</td>
</tr>
</tbody>
</table>
occur in both the venous and arterial vessels; venous thrombosis is the most common manifestation. Consequently, pulmonary embolism is the most frequently reported fatal complication associated with HIT-II.

Diagnosis and confirmation of HIT is difficult and lengthy, with laboratory test results often taking hours to days to obtain. HIT should be suspected in patients with 1 or more of the following factors: unexplained decrease in platelet counts every 1 to 2 days during the first 10 days of therapy, a 30% or greater decline in platelet count, platelet count less than $150 \times 10^9/L$, unexplained thromboembolism, skin necrosis, or transient global amnesia.

Once HIT is suspected, laboratory tests should be used to confirm the diagnosis. Three tests are commonly used to confirm the presence of HIT. The platelet aggregation test and serotonin release assay are functional tests used to determine platelet activation; a positive result from either should confirm the diagnosis. These tests are problematic and difficult to perform, however, and they require specially trained laboratory personnel. In addition, the sensitivity and specificity of these assays are dependent on the quality of donor platelets. The third test available is an enzyme-linked immunosorbant assay (ELISA) that detects antibodies to the heparin-PF4 complex. The results obtained from ELISA tests, however, should be interpreted with caution. Differing results have been obtained with various commercially available ELISA kits. Further, the ELISA tests have yielded false-positive results for the presence of heparin-PF4 antibodies in patients who do not have active thrombocytopenia or unexplained thrombosis.

**Therapeutic Alternatives**

Because of the increased risk of thrombosis-related morbidity and mortality, patients with suspected HIT require alternative anticoagulation. For all patients, heparin therapy should be discontinued before an alternative anticoagulant is started. Use of low-molecular-weight heparin is discouraged because of its cross-reactivity with HIT-IgG. Warfarin has been studied for use in patients with HIT; however, warfarin is risky to use in these patients. Warfarin inhibits the production of protein C, an intrinsic anticoagulant, which can lead to microvascular thrombosis and ultimately to venous gangrene of the limbs.

**Danaparoid**

Danaparoid sodium, a heparinoid, is a mixture of heparan sulfate, dermatan sulfate, chondroitin sulfate, and low-molecular-weight heparin. Even though this drug is not indicated for treatment of HIT, danaparoid is a useful alternative to heparin for treating patients with HIT. Danaparoid primarily inhibits factor Xa, with minor inhibition of factor IIa (see Figure). When HIT is suspected, danaparoid is dosed in patients with normal renal function at 750 anti-Xa units subcutaneously twice daily for 7 to 10 days; in patients with active thrombosis, the dose is typically doubled to 1500 anti-Xa units subcutaneously daily.
units given via intravenous bolus, then 1500 anti-Xa units subcuta-
neously twice daily for 7 to 10 days. Dose adjustments should be individu-
alized on the basis of the patient’s renal function and body weight.

Although danaparoid is effective in treating patients with HIT, the use of danaparoid in such patients is associated with potential problems. Cross-reactivity with HIT-IgG is seen in 10% to 20% of HIT patients treated with danaparoid, ultimately prolonging the thrombocytopenia/throm-
bosis syndrome. Reversal of anticoagulation can be problematic because of the lack of an antidote and the long half-life of danaparoid (Table 2). Therapeutic monitoring is difficult because of the lack of availability of anti-Xa assays. Finally, danaparoid can have enhanced and prolonged anticoagulation effects in patients with renal insufficiency.

**Lepirudin**

Another alternative for the treatment of HIT is lepirudin. Lepirudin is a recombinant form of hirudin, a protein found in the saliva of leeches. Lepirudin directly inhibits factor IIa (thrombin), thus preventing the formation of fibrin and activation of factors V, VII, and XII and protein C (see Figure). Further, inhibition of thrombin prevents platelet aggrega-
tion, which is beneficial in HIT patients. Lepirudin can be used in patients who require anticoagulation for cardiac surgeries, for prophylaxis of HIT, and to treat active thrombosis. In patients with HIT, a lepirudin bolus dose of 0.4 mg/kg is given intravenously, followed by a continuous intravenous infusion of

---

**Table 2.** Comparison of argatroban, danaparoid, and lepirudin for use in heparin-induced thrombocytopenia (HIT)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Argatroban</th>
<th>Danaparoid sodium</th>
<th>Lepirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical constitution</strong></td>
<td>Synthetic derivative of L-arginine</td>
<td>Heparinoid (dermatan sulfate, heparan sulfate, and chondroitin sulfate)</td>
<td>Recombinant protein form of hirudin</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Inhibits factors Xa and IIa (ratio 28:1)</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Initiate infusion with 2 µg/kg per minute; adjust dose to an aPTT of 1.5-3 times baseline (not to exceed 100 seconds) or to a maximum of 10 µg/kg per minute. Hepatic insufficiency: 4-fold increase in normal dose</td>
<td>Suspected HIT: 750 anti-Xa units subcutaneously twice daily. Active thrombosis: 1500 anti-Xa units intravenous bolus, then 1500 anti-Xa units subcutaneously twice daily (normal renal function)</td>
<td>0.4 mg/kg bolus; then 0.15 mg/kg per hour (up to 16.5 mg/h); reduce both bolus and infusion dose by 50% if serum creatinine level is 133 to 177 µmol/L (1.5 to 2.0 mg/dL)</td>
</tr>
<tr>
<td><strong>Route of elimination</strong></td>
<td>Hepatic</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>40 minutes</td>
<td>24 hours</td>
<td>1.3 hours</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>40 minutes</td>
<td>Prolonged</td>
<td>2-107 hours</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>80 minutes</td>
<td>24 hours</td>
<td>1.3 hours</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>aPTT</td>
<td>Antifactor Xa assay</td>
<td>aPTT</td>
</tr>
<tr>
<td><strong>Immune effects</strong></td>
<td>None known</td>
<td>Cross-reaction to HIT IgG</td>
<td>Antibodies to drug can increase half-life</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per milligram</td>
<td>$2.99</td>
<td>$2.45†</td>
<td>$2.79</td>
</tr>
<tr>
<td>Per day</td>
<td>$600</td>
<td>$67</td>
<td>$700</td>
</tr>
</tbody>
</table>

aPTT indicates activated partial thromboplastin time; IgG, immunoglobulin G.

†750 units of danaparoid equals 55 mg of the drug.
Pharmacology

0.15 mg/kg per hour (up to 16.5 mg/h maximum). Lepirudin is renally eliminated, so patients with renal insufficiency will have prolonged elimination and anticoagulant effect. Dosing of lepirudin should be adjusted on the basis of the serum creatinine level. Both the bolus and infusion doses should be reduced by 50% if the serum creatinine level is between 133 and 177 µmol/L (1.5-2.0 mg/dL), by 70% if between 186 and 265 µmol/L (2.1-3.0 mg/dL), and by 80% if between 274 and 530 µmol/L (3.1-6.0 mg/dL). Lepirudin should not be used in patients with a serum creatinine level greater than 530 µmol/L (6.0 mg/dL). Unlike danaparoid, lepirudin does not cross-react with HIT-IgG; however, lepirudin can mediate a direct immunologic response in 50% of patients with HIT, thus prolonging the half-life and extending the anticoagulant effect.

Argatroban

Argatroban was recently approved for prophylaxis of thrombosis in patients with HIT and as an anticoagulant in patients undergoing percutaneous coronary intervention who have or are at risk for HIT. Argatroban is derived from L-arginine, which directly and reversibly binds to the catalytic site of either free or clot-bound thrombin. In patients with normal hepatic function, argatroban therapy for HIT should be initiated at 2 µg/kg per minute intravenously. Dosing is then adjusted either to an activated partial thromboplastin time (aPTT) of 1.5 to 3 times baseline (aPTT should not exceed 100 seconds) or a maximum dose of 10 µg/kg per minute intravenously. For patients with HIT who are undergoing percutaneous coronary intervention, an initial bolus dose of 350 µg/kg is given intravenously over 3 to 5 minutes, followed by continuous intravenous infusion of 25 µg/kg per minute. Dosing is adjusted to maintain an activated clotting time (ACT) between 300 and 450 seconds. As a general guideline in percutaneous coronary intervention, when the ACT is less than 300 seconds, an additional intravenous bolus dose of 150 µg/kg is given and the infusion dose should be increased to 30 µg/kg per minute. When the ACT is greater than 450 seconds, the infusion dose of argatroban should be decreased to 15 µg/kg per minute. The ACT should be checked 5 to 10 minutes after any dosage adjustment.

Pharmacokinetic and pharmacodynamic studies have revealed that renal function, age, and sex do not have a clinical effect on metabolism, distribution, elimination, or anticoagulation of argatroban. Hepatic metabolism of argatroban occurs primarily via cytochrome P-450 enzyme 3A4, so dosage modification is necessary in patients with hepatic insufficiency (Table 2). Steady-state blood levels and anticoagulant effect of argatroban are usually obtained 1 to 3 hours after initiation of therapy. Both steady-state concentrations and anticoagulant effects are well correlated and predictable for dosages up to 40 µg/kg per minute. No significant interactions between argatroban and aspirin, erythromycin, acetaminophen, digoxin, lidocaine, or warfarin have been demonstrated or reported. The use of argatroban and warfarin concomitantly, however, can increase the risk of bleeding, so the international normalized ratio, aPTT, and signs of overt bleeding should be monitored carefully when these agents are used together. Furthermore, no safety or efficacy data are available on the combined use of argatroban with thrombolytic agents, antiplatelet agents, or other anticoagulants; caution must be exercised when argatroban is used concomitantly with these agents because of the increased risk of bleeding. The use of argatroban is relatively safe and has been associated with few adverse events. The most frequent adverse effects reported are bleeding, dyspnea, and hypotension. Argatroban does not elicit formation of antibodies or have cross-sensitivity to HIT-IgG antibodies. However, argatroban is contraindicated in patients with evident major bleeding or with a hypersensitivity to argatroban. Laboratory monitoring of argatroban for HIT therapy generally should be initiated 2 hours after the initial dose by measuring aPTT; 2 hours will allow enough time for the anticoagulation effects of argatroban to reach steady state. The desired therapeutic target of argatroban therapy is an aPTT 1.5 to 3 times baseline aPTT, not to exceed 100 minutes. In patients undergoing percutaneous coronary intervention, therapy is monitored by using ACT with a therapeutic target range between 300 and 450 seconds. Although no antidote is available for overdoses of argatroban, over-anticoagulation can be managed either by decreasing the infusion rate or discontinuing argatroban infusion until a therapeutic aPTT is achieved; reversal of anticoagulant effects can be seen within 2 to 4 hours subsequent to discontinuation of therapy. Intravenous solutions of argatroban are stable in ambient conditions.
indoor light at temperatures between 15°C and 30°C for 24 hours and for 48 hours if stored at 2.2°C to 7.8°C away from light. Exposure to direct sunlight should be avoided to prevent photodegradation.

In a multicenter, nonrandomized, open-label study, the safety and efficacy of argatroban were assessed in 304 patients with HIT. Patients had either uncomplicated HIT (n = 160) or HIT with thrombotic syndrome (HITTS; n = 144) and were compared with 193 historical control subjects (patients treated with the standard of care when HIT was diagnosed). Baseline characteristics for both groups were similar except for age (patients in the control groups were significantly younger than the patients in their respective treatment groups). To be included in the study, the patients had to have documented thrombocytopenia (platelet count <100 × 10^9/L, or 50% reduction in platelet count after initiation of heparin therapy). Patients were excluded if they had a history of aneurysms, hemorrhagic or thrombotic stroke, or lumbar puncture within the past 7 days, an unexplained aPTT greater than 2 times baseline, or documented coagulation or bleeding disorders unrelated to HIT.

The treatment group received the standard dosing HIT protocol of 2 µg/kg per minute of intravenous argatroban, with a dosage adjustment to maintain an aPTT of 1.5 to 3 times baseline levels. The primary efficacy end point of the study was a composite of all-cause death, all-cause amputation, or new thrombosis within 37 days of baseline. Secondary end points were death caused by thrombosis, any new thrombosis, achievement of anticoagulation, and resolution of thrombocytopenia.

Platelet counts were not significantly different between the treatment and historical control groups. Mean duration of treatment with argatroban was 6 days. The composite primary end point was reached by significantly fewer patients treated with argatroban than control subjects with HIT (25.6% vs 38.8%, P = .01), but no significant difference was found between the percentages of patients reaching the composite primary end point in the argatroban group and the HITTS group. Time to first event for the composite end point significantly favored argatroban treatment over standard therapy (ie, it took longer for the first event to occur in the argatroban group) in both HIT and HITTS arms of the trial (P = .01). All-cause mortality did not differ significantly between treatment and control groups; however, argatroban treatment significantly reduced death caused by thrombosis compared with control therapy (P = .005 for HIT group, P < .001 for HITTS group). In addition, new thrombosis was significantly lower in both argatroban treatment groups than in the control groups (P < .001 for HIT group, P = .04 for HITTS group). Thrombocytopenia was resolved by day 3 in at least 53% of patients treated with argatroban; overall, resolution of thrombocytopenia during the full treatment interval occurred in 81% of argatroban-treated patients in the HIT arm and 69% in the HITTS arm compared with 41% of control patients in the HIT arm and 50% of control subjects in the HITTS arm (no statistics reported). By day 3, mean platelet counts increased by approximately 50 × 10^9/L in argatroban-treated patients compared with a decline of 20 × 10^9/L to 30 × 10^9/L in control subjects (P < .001). Anticoagulation was adequately achieved in at least 83% of treated patients within 4 to 5 hours after initiation of therapy.

Major bleeding rates were similar in the treatment and control groups. The most common adverse effects experienced in the argatroban-treated group were diarrhea and pain.

**Conclusion**

HIT is a serious, life-threatening complication. The use of an alternative anticoagulant is necessary to prevent further morbidity and mortality in HIT patients. The addition of argatroban, a direct thrombin inhibitor, has increased the available therapeutic options for HIT.

Argatroban may be a more practical agent for HIT therapy than danaparoid and lepirudin because its shorter half-life allows for rapid onset and reversal of anticoagulant effects. In addition, argatroban may be better than danaparoid for treating HIT because of argatroban’s lack of cross-reactivity with HIT-IgG, and argatroban may be better than lepirudin because of argatroban’s lack of adverse immunologic reactions. Because the pharmacokinetic and clinical effects of argatroban are unaffected by renal function, argatroban may be the most sensible agent to use in renally compromised patients. However, argatroban will have prolonged anticoagulation and elimination in patients with hepatic insufficiency.

On a milligram-to-milligram basis, the cost of argatroban is comparable to the costs of danaparoid and lepirudin (Table 2); however, the total
daily cost of therapy favors danaparoid. Danaparoid therapy would be approximately $67/day, compared with $600/day for argatroban (based on a patient weighing 70 kg and standard dosing for HIT). Interestingly, the cost of lepirudin would be approximately $700/day based on the preceding criteria, indicating that argatroban is a more cost-effective therapeutic choice than lepirudin. Although argatroban improves clinical outcomes in patients with HIT, it is unclear whether argatroban is superior to the other available agents because of the lack of head-to-head trials. Further clinical experience and studies on comparative efficacy and safety are needed to determine the most appropriate agent for treating HIT.

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References
Argatroban: A New Treatment Option for Heparin-Induced Thrombocytopenia
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