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Benefit-Risk Assessment of Treatments for Heparin-Induced Thrombocytopenia

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Abstract

Patients with heparin-induced thrombocytopenia (HIT) are at high risk of thrombosis and should be treated with alternative anticoagulant therapy to reduce complications. The current treatment of choice is one of the approved direct thrombin inhibitors, argatroban or lepirudin. These drugs have been proven to be safe and effective in multicentre clinical trials where dosage regimens have been

established for prophylaxis and treatment of thrombosis. Argatroban has also been tested and approved for use in invasive cardiology procedures in the HIT patient. Dosage regimens for other clinical uses, such as cardiac surgery, have not yet been established for either drug. The safety and effectiveness of the thrombin inhibitors is dependent on their use according to established guidelines. Other treatment options that may be effective for the patient with HIT include dextran, plasmapheresis, intravenous gammaglobulin and aspirin (acetylsalicylic acid). Although used historically, these options have not been tested in rigorous clinical trials. For life- and limb-threatening thrombosis, thrombolytic agents and/or surgery may provide benefit. Because the risk of bleeding is high from these procedures, they should be performed only by an experienced practitioner. Several studies have shown that patients with HIT requiring continued anticoagulation are best managed with a warfarin derivative initiated while under full anticoagulation with a thrombin inhibitor. There is a risk of skin necrosis and bleeding if guidelines for dose administration and monitoring of warfarin are not followed. Subsequent use of heparin or a low molecular weight heparin after resolution of the clinical episode of HIT can be hazardous, particularly within the first 3 months. If laboratory testing is negative, heparin may be cautiously reinstituted for short-term use (1–2 hours) with monitoring for platelet count decrease and thromboembolism. The pregnant patient with HIT requiring anticoagulation represents a particular challenge, where there is no drug of choice at present. Although today there are realistic treatment options for the patient with HIT, the morbidity and mortality associated with this disease have not been eliminated. Awareness and early treatment of HIT remain important components of the clinical care for patients exposed to heparins. Future therapeutic developments based on a better understanding of the pathophysiology of HIT may further improve clinical outcomes. Despite some limitations, the current treatment options for patients with HIT provide unparalleled benefit compared with the treatment options available only a few years ago.

1. Heparin-Induced Thrombocytopenia (HIT)

1.1 Pathophysiology

A transient thrombocytopenia caused by a benign, nonimmunological mechanism can occur upon exposure to heparin. By convention this is called heparin-induced thrombocytopenia (HIT) type I. Heparin can also cause the immune-mediated syndrome HIT type II, which is associated with limb-threatening thrombosis and death. HIT type II occurs in approximately 2% of all patients exposed to heparin by any parenteral route (intravenous 3–5%; subcutaneous, heparin-locks on arterial or venous lines, or heparin-bonded intravascular devices at a lesser percentage). Low molecular weight heparins are capable of inducing this syndrome as well.[1-3]

Understanding of the pathophysiological processes that underlie the HIT type II syndrome has evolved over the past 45 years. The first report of this disorder was in 1958 by Weismann and Tobin.[4] They observed a paradox in which heparin therapy was associated with arterial thromboembolism. This was followed by a report by Roberts et al.[5] in 1964, which confirmed the earlier report. In 1969 Natelson et al.[6] reported thrombocytopenia in a patient treated with heparin. It was stated in this report that when the patient's platelet-rich plasma was supplemented with heparin, a fall in platelet count resulted as compared with control platelet-rich plasma. However, the patient's serum plus heparin did not cause a

Table I. Criteria for suspecting heparin-induced thrombocytopenia

Progressive unexplained fall in platelet counts performed every 1–2 days during the first 10 days of therapy:
Baseline count:
pre-heparin therapy
highest count postoperatively
Significant fall defined as:
30% or greater fall from any level *or*
platelet count decreased to <100 000/μL
Onset of new thromboembolism with or without fall in platelet count that is unexplained
Extension of previous thrombotic problem
Skin necrosis
Transient global amnesia
Disseminated intravascular coagulation with no apparent cause

fall in platelet count in control platelet-rich plasma. Though this appeared to be the first case, wider attention to this problem was drawn in a report by Bell and associates[7] in a 1976 prospective study. Since 1973 there have been numerous reports showing that either thrombocytopenia or thrombosis, or both, may occur with heparin therapy, with antibodies to heparin-platelet factor 4 (PF4) complexes being eventually determined as the factor mediating platelet destruction.[8-12]

The current concept is that some patients with HIT type II develop antibodies to heparin complexed to PF4 or occasionally other substances such as neutrophil activating peptide-2 or interleukin 8 and possibly other heparin-binding proteins. These complexes are the antigens which bind to an IgG_2 antibody or other immunoglobulin such as IgA and IgM. The Fc portion of the antibodies then binds to platelet Fc receptors, activating the platelet and inducing a hypercoagulable state, causing platelet destruction.[13-16] Activation of macrophages, neutrophils and monocytes as well as endothelial cells may also occur.[17-19]

1.2 Diagnosis

HIT type II is a clinical diagnosis that should be confirmed with laboratory testing. The diagnosis of HIT is made by strong clinical findings, including a return of platelet counts to normal following cessation of heparin therapy.

Criteria for the clinical suspicion of heparin are important, since heparin should be stopped and a substitute anticoagulant introduced as soon as the diagnosis is suspected. Factors that may lead to suspecting the diagnosis of HIT are listed in table I.[20-22]

The adverse events that arise as a result of HIT can be responsible for the generation of numerous symptoms and signs. To aid in the diagnosis of HIT, thrombotic complications that have been reported in patients with HIT are listed in table II. It is obvious that this can be a devastating clinical problem, threatening both limb and life in up to 50% of affected patients.[23-26]

Laboratory testing, though important, does not guide initial therapeutic measures because of the necessity for immediate intervention once HIT is suspected. Results of laboratory tests are usually not available for several hours or even days. The importance of laboratory testing is to confirm the diag-

Table II. Thrombotic complications reported in heparin-induced thrombocytopenia

Arterial thrombosis
Aorta
Iliac artery
Femoral artery
Renal artery
Mesenteric artery
Coronary artery
Cerebral artery
Spinal artery
Livedo reticularies
Venous thrombosis
Pulmonary embolism
Superficial and deep vein
Cerebral sinus
Adrenal vein
Venous limb gangrene (phlegmasia cerulea dolens)
Vascular graft occlusion
Intracardiac thrombosis
Coronary artery bypass grafts
Ventricular mural thrombus
Mechanical valve
Atrial
Microcirculatory thrombosis
Without warfarin therapy
With warfarin therapy (warfarin-induced necrosis)

nosis and to guide future therapy. Patients who have a positive functional test for HIT (see section 3) are at great risk for recurrence should they be re-exposed to heparin before the antibody disappears and certainly within the first 90 days of diagnosis.[27-29]

1.3 Confirmatory Testing

Three types of tests are commonly in use for the diagnosis of HIT. With either of the two functional tests based on platelet activation (platelet aggregation test [PAT] and serotonin release assay [SRA]), a positive result confirms the diagnosis. The third method is an ELISA, for which there are two commercially available kits. These immunoassays detect antibodies to the complex of PF4 bound to either heparin or to polyvinyl sulfonate molecules.

The precise methodology for the SRA is available, but a variety of methods have been described for the PAT.[30-34] Caution is advised for interpreting results from any laboratory test for HIT, as no test is optimal. These tests are complicated and are best performed by skilled laboratory technicians who have experience working with platelets. To ensure sensitivity and specificity of these functional platelet assays, it is most important to use sensitive donor platelets. In addition, specific protocols must be followed for proper handling of platelets and for positive and negative controls on the assay system. A further limitation of the SRA includes handling of radioactive material.

The clinical significance of the presence of heparin-PF4 antibodies as detected by the ELISA methods is not always clear, for example, patients who have the ELISA antibody but no thrombocytopenia and/or unexplained heparin-related thrombosis have been observed.[30] Additionally, ELISA is not 100% sensitive, in that some patients who are positive by a sensitive functional assay (SRA) are negative by the ELISA method.[35] In some instances these could be false-positive functional assays, especially with the aggregation method. Furthermore, comparison of the two commercial ELISA kits has shown some disagreement in results.[33,36] ELISA testing is becoming more commonly used because it is easy to perform, no specific platelet donors are required, there is no radiation handling, and the turnaround time of the test result is relatively fast. Nevertheless, users of the ELISA must be aware of the limitations of this test in relation to clinical relevance. The functional assays provide a more definitive answer.

The process of confirmation of the diagnosis of HIT by a combination of clinical findings and one or more laboratory tests is still undergoing investigation. A report by Pouplard et al.[37] illustrates some of the problems and proposes possible solutions. We have used the following testing regimen with success over the years: a functional test should be done first; if the test is positive, no further testing is required as a rule. If the functional test is negative, and the clinical suspicion is still strong, an ELISA should be performed; if positive, the patient has confirmed HIT. A positive ELISA should not be used as the only test result; it should be confirmed by a functional test. Repeat testing on subsequent days may be valuable if the functional assay is negative. We have reservations about using a negative ELISA to exclude the diagnosis of HIT unless the clinical probabilities are very weak. Combining laboratory testing with clinical criteria is important for the diagnosis of HIT.

2. Therapeutic Interventions

2.1 Overview

Even though HIT represents a unique hypercoagulable state with a spectrum of localised or disseminated intravascular thromboses related to endothelial damage, as well as to activated circulating platelets and clotting factors, thromboembolism is treated by conventional medical and surgical modalities. The only difference is that heparin is not to be given and LMWHs are to be avoided except in unusual circumstances where they have been shown to be nonreactive with the patient's serum *in vitro* and argatroban or lepirudin are not available.

A practical approach to management of HIT patients is shown in table III. There are usually a number of critical decisions to be made early in the course of HIT. It is prudent to obtain urgent consultative help from knowledgeable specialists when the

diagnosis is suspected, particularly if there is any doubt.[22] A consultation with experts in tertiary care centres may be advisable in difficult and complicated cases.

Patients with HIT are at an extremely high risk of developing thrombosis; yet it is also not always possible to identify patients with thrombosis. Thus, it is advisable to treat all patients with HIT prophylactically for thrombosis. The benefit is that thrombosis and its complications, which can be as extreme as amputation and death, are avoided; the risk is only that of bleeding due to the action of the treatment drug. Choosing an effective antithrombotic drug and using a proven dosage regimen can minimise this risk. The risk of death, new thromboembolic complications and limb amputation is highest in the period between diagnosis of HIT and the start of treatment.[38]

For most patients, stopping heparin and instituting substitute therapy, with or without an oral anticoagulant drug (OAC) for longer-term treatment, is the basic approach for treatment of heparin antibody-induced thrombosis. Some patients may require a combination of treatment modalities. Patients with ischaemic limbs or organs may require more drastic measures than substitute anticoagulant therapy alone (table IV).

Table III. Management of heparin-induced thrombocytopenia (HIT) and HIT-associated thrombosis (suspected)[a]

Consultation when there is any doubt
Stop all heparin, including line flushes, coated materials, etc.
Administer a substitute anticoagulant – consultation advised
Order laboratory testing for confirmation – consultation advised
Management of thrombosis associated with ischaemia – consultation advised
Thrombus removal for severe ischaemia by surgical or medical (local or systemic thrombolytic therapy) means
Long-term management plan – warfarin derivative when indicated (no loading dose; safest to start at 5 mg/day or less while still anticoagulated with substitute drug)
Future – a history of HIT in the past 3 months should be a reminder to test for HIT before giving heparin. Recent heparin therapy should prompt close monitoring for HIT. It is important to know if a patient has had heparin therapy within the last 3 months, as this imparts an additional risk of potentially developing early onset HIT

a This is a general guideline only; management strategies are still in evolution.

Table IV. Specific therapeutic modalities for the treatment of heparin-induced thrombocytopenia

Antithrombin drugs
lepirudin
argatroban
Surgical thrombectomy
Vena caval interruption
Thrombolytic therapy
Plasmapheresis
Intravenous gammaglobulin
Antiplatelet agents
Warfarin derivative[a]
Low molecular weight heparins[b]

a For long-term management, but should not be used in the absence of prior therapy with a thrombin inhibitor drug.

b To be used only under very specific circumstances with appropriate safeguards.

2.2 Dextran

In the past 20 years a variety of drugs have been used to treat thromboembolic complications in patients with HIT.[39-43] The first to be used was dextran 40 or dextran 70. Variable results were obtained with regard to anticoagulation and reduction of thrombotic events. In addition, anaphylactic or anaphylactoid reactions occurred with dextran, which required very careful monitoring. In a more recent prospective study in which dextran 70 was compared with danaparoid sodium there appeared to be a definite benefit from both drugs, but danaparoid sodium was superior.[39] Since the advent of newer drugs, which have been evaluated by prospective controlled studies, therapy with dextran has become outmoded. Newer drugs (thrombin inhibitors) are probably much more effective than dextran.

2.3 Danaparoid Sodium

Danaparoid sodium is a mixture of non-heparin polysulphated glycosaminoglycans (84% heparan sulphate, 12% dermatan sulphate, 4% chondroitin sulphate and <1% LMWH). Although related to heparin in structure, danaparoid sodium differs from heparin in degree of sulphation and molecular weight. Over the last 12 years danaparoid sodium has been used in numerous patients with HIT (708 reported treatment episodes) and in varied clinical

settings such as haemodialysis, plasmapheresis, treatment of pulmonary emboli, venous or arterial thrombosis and unstable angina, and during therapy with the intra-aortic balloon pump.[44-47] Overall, there were 93% successful evaluable treatments and 7% failures. In one comparative clinical study, danaparoid sodium plus warfarin was more effective than dextran 70 plus warfarin at normalising the thrombocytopenia and resolving thromboembolic events in patients with severe thromboembolic complications.[39] With danaparoid sodium, there was complete clinical recovery from 56% of thromboembolic events compared with 14% after dextran 70 ($p = 0.02$). Clinical recovery with danaparoid sodium was complete or partial in 86% of thromboembolic events compared with 53% after dextran 70 ($p = 0.03$).

Although danaparoid sodium is useful, it has limitations, which include positive platelet reactions in about 15% of HIT patients,[48,49] a long half-life (about 25 hours), monitoring assays that are not commonly available, lack of an antagonist, and dosage guidelines that are not well established for cardiac surgery, which has led to significant postoperative bleeding.

Danaparoid sodium had been approved by the US FDA for the prophylaxis of postoperative deep vein thrombosis that may lead to pulmonary embolism in patients undergoing elective knee replacement surgery. It was used off-label for treatment of patients with HIT in the US. In future, however, therapy with danaparoid sodium in the US will not be possible because of its withdrawal from the market by its manufacturer. Danaparoid sodium remains approved and available in Europe for prophylactic and therapeutic anticoagulation of patients with HIT.

2.4 Thrombin Inhibitors

The modalities of therapy available for patients with HIT are given in table IV. Well designed clinical studies have shown that anticoagulation with the thrombin inhibitors argatroban and lepirudin significantly reduces the risk of thrombosis and thromboembolic complications (new thrombosis, amputation, death) associated with HIT. This benefit was achieved with an acceptable safety profile.

A comparison between argatroban and lepirudin is given in table V. Aside from several differences, there are many similarities between these two drugs. Thrombin inhibitors are potent inhibitors of both free and clot-bound thrombin. They directly and selectively block thrombin with little or no effect on related serine proteases. They are not inactivated by PF4, do not cross-react with HIT antibodies,[48] and do not potentiate HIT. At present, no specific antidote is available for this drug class. Excessive anticoagulation can be controlled by discontinuing drug or decreasing its infusion dose. There are limited case reports of use of haemofiltration to remove excessive drug.[50,51]

2.4.1 Argatroban

Argatroban is a synthetic thrombin inhibitor derived from L-arginine. It binds tightly yet reversibly to thrombin. Individuals receiving prolonged or repeated administration show no generation of antibodies and no enhancement or suppression of anticoagulant response.[52] (See Lewis et al.[53] and McKeage and Plosker[54] for a review of argatroban.)

Plasma drug concentrations of argatroban increase proportionally with doses up to 40 μg/kg/min. The dose-response curve is gentle and predictable, allowing for a wide margin of safety during

Table V. Comparison between argatroban and lepirudin

Argatroban	Lepirudin
Shorter half-life	Longer half-life
Anticoagulant response rapidly reversed	Anticoagulant response slowly reversed
No antibody formation	Antibodies generated that delay elimination or decrease anticoagulant activity
Bleeding complications	Bleeding complications
Metabolised in the liver	Cleared via the kidney
Requires dose adjustment in liver disease patients	Requires dose adjustment in renal disease patients
Monitored by aPTT; monitored by ACT for percutaneous coronary intervention	Monitored by aPTT

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time.

dose titration. Steady-state levels of drug and anticoagulant effect are attained within 1–3 hours (faster with a loading bolus) and maintained with low intra- and intersubject variability. On stopping infusion, plasma argatroban levels are rapidly reversed (half-life 39–51 minutes), and coagulation parameters generally return to pretreatment values within 2–4 hours.[53,55,56]

Argatroban is hepatically metabolised. Patients with moderate hepatic impairment, compared with healthy volunteers, have an approximate 4-fold decrease in drug clearance (to 1.5 mL/min/kg) and an approximate 3-fold increase in elimination half-life (to 152 minutes).[53,55] Reversal of anticoagulation upon discontinuing drug infusion may take at least 6 hours and perhaps more than 20 hours in hepatically impaired patients. Age, sex and renal function exert no clinically significant effects on the pharmacokinetics or pharmacodynamics of argatroban in adults.[53,55,56] No special adjustment in initial argatroban dosage is needed for patients with renal impairment. Drug interactions with thrombolytics and warfarin derivatives may affect the risk of bleeding. No pharmacokinetic or pharmacodynamic drug interactions have been reported between argatroban and aspirin (acetylsalicylic acid), erythromycin, paracetamol (acetaminophen), digoxin or lidocaine.[53]

Argatroban anticoagulant therapy has been evaluated in patients with clinically diagnosed HIT in three prospective, multicentre, open-label studies (ARG-911, ARG-915 and ARG-915X).[57,58] Across the studies reported, 754 patients received argatroban therapy on 809 separate occasions. Outcomes were compared with those of 193 historical controls.

The argatroban-treated patients received continuous intravenous argatroban, starting at a dose of 2 μg/kg/min. Dosage was adjusted (10 μg/kg/min maximum) until the activated partial thromboplastin time (aPTT) was 1.5–3 times the baseline aPTT value (not to exceed 100 seconds). The aPTT was measured daily and 2 hours after each dosage adjustment. Patients typically remained on argatroban for 14 days.

In the ARG-911 study,[57] the composite endpoint (all-cause death, all-cause amputation, or new thrombosis within a 37-day period) was reduced significantly in argatroban-treated patients (n = 304) versus controls with HIT (n = 193) [25.6% vs 38.8%; p = 0.014]. In patients with HIT and thrombosis (HITTS), the composite endpoint occurred in 43.8% of argatroban-treated patients (n = 144) compared with 56.5% of controls (n = 46) [p = 0.13]. Significant between-group differences by time-to-event analysis of the composite endpoint favoured argatroban treatment in HIT (p = 0.010; hazard ratio 0.60; 95% CI 0.40–0.89) and HITTS (p = 0.014; hazard ratio 0.57; 95% CI 0.36–0.90).

Argatroban therapy, compared with control, significantly reduced death due to thrombosis in each study arm (HIT p = 0.005; HITTS p < 0.001). There were no between-group differences in all-cause mortality. The incidence of amputation was similar between groups. Argatroban therapy also significantly reduced the percentage of patients experiencing new thrombosis in each study arm (HIT p < 0.001; HITTS p = 0.044). Compared with controls, argatroban-treated patients had a significantly more rapid rise in platelet counts. Resolution of thrombocytopenia occurred by day 3 in 53% of argatroban-treated patients with HIT and 58% of patients with HITTS.

Efficacy results from the ARG-915 study[58] (HIT n = 125; HITTS n = 139) confirm and support the findings from the ARG-911 study, where the positive benefits on the composite endpoint were driven predominantly by significant reduction in new thrombosis.

In the ARG-911 study, major bleeding occurred in 6.9% (21/304) argatroban-treated patients, compared with 6.7% (13/193) historical controls. In each group, there were two fatal bleeding events. One patient experienced a fatal intracranial haemorrhage 4 days after discontinuation of argatroban and following urokinase and warfarin therapy; one historical control also experienced a fatal intracranial haemorrhage. Minor bleeding rates were similar between the groups (41%).

In ARG-915, argatroban was also generally well tolerated. Major bleeding occurred in ten (3.8%) argatroban-treated patients, and no patient experienced intracranial bleeding.

Across these studies plus the extension study (ARG-915X), 55 patients with HIT underwent anticoagulant therapy with argatroban on more than one occasion for the prophylaxis or treatment of thrombosis.[58] The dosage and duration of argatroban therapy were similar between patients upon repeat exposure (repeat group n = 55) and patients on their first exposure (initial group, n = 754). Event rates in the repeat group were less than with those in the initial group for the composite endpoint (20% vs 34%), new thrombosis (3.6% vs 11.1%) and major bleeding (3.6% vs 6.6%). Patients re-exposed to argatroban had no allergic reactions or apparent differences, relative to the initial group, in adverse experiences.

On the basis of these data, argatroban received approval in the US as an anticoagulant for prophylaxis or treatment of thrombosis in HIT patients and in Canada as an anticoagulant for HIT patients who, in the opinion of their attending physician, require anticoagulation.

2.4.2 Lepirudin

Lepirudin is a recombinant hirudin, derived from the natural hirudin from the leech (*Hirudo medicinalis*). It binds tightly to thrombin with very slow dissociation such that it appears to act as an irreversible inhibitor.[59] Approximately 50% of lepirudin-treated HIT patients generate antibodies that may enhance its anticoagulant activity, necessitating careful monitoring to avoid bleeding complications.[60,61]

The terminal half-life of lepirudin is 1.3 hours. Lepirudin is renally excreted and should be used with caution in patients with renal insufficiency and avoided in patients with acute renal failure or on haemodialysis. No dose adjustment in necessary in patients with hepatic failure. Drug interactions with thrombolytics and warfarin derivatives may affect the risk of bleeding.[62]

Lepirudin was evaluated for safety and efficacy in 198 patients with HIT confirmed by laboratory testing. Lepirudin significantly improved clinical outcomes in HIT patients, compared with historical controls. However, there was an associated major bleeding rate (i.e. bleeding events requiring transfusion) higher than that of controls (p = 0.02).[38,63,64]

In the Heparin-Associated Thrombocytopenia (HAT)-1 trial,[63] 82 patients were given one of four intravenous regimens: 0.4 mg/kg bolus followed by 0.15 mg/kg/h in HITTS patients (n = 51); 0.2 mg/kg bolus followed by 0.1 mg/kg/h in HITTS patients receiving thrombolysis (n = 5); 0.1 mg/kg/h in HIT patients (n = 18); 0.25 mg/kg bolus and 5mg boluses as needed during cardiopulmonary bypass surgery (n = 8). Outcomes of 71 patients were compared with those of a historical control group of 120 patients. The incidence of the combined endpoint (death, amputation, new thromboembolic complications) was significantly reduced in lepirudin-treated patients (p = 0.014). Effective anticoagulation was reported in 82% of the HIT patients. Platelet counts increased rapidly in 88.7% of treated patients. Bleeding rates were similar in both groups.

In the HAT-2 trial,[64] 112 patients with HIT confirmed by laboratory testing received treatment by one of three dosage regimens for 2–10 days or longer: 0.4 mg/kg bolus followed by 0.15 mg/kg/h for treatment of thrombosis (n = 65); 0.2 mg/kg followed by 0.1 mg/kg/h (n = 4) in conjunction with thrombolytic therapy; 0.01 mg/kg/h (n = 43) for prophylaxis. Outcomes of 95 patients compared with those of 120 historical control patients showed aPTT >1.5 times baseline; effective anticoagulation was reported in 75% of the HIT patients. Platelet count normalised by day 10 in 69% of treated patients. Within 35 days after HIT confirmation fewer lepirudin-treated patients than historical control patients experienced outcome events (p = 0.12). Bleeding events in the lepirudin group were more frequent (44.6% vs 27.2%; p = 0.0001).

Meta-analysis of the HAT-1 and HAT-2 trials [38] showed that the primary combined endpoint occurred in 22.1% of lepirudin-treated patients (n = 113), which was consistently lower than in the historical control patients (n = 91) [p = 0.004]. This was primarily due to the reduction in new thromboem-

bolic events. The cumulative risk of new thromboembolic complications after 35 days of treatment was 10.1% with lepirudin versus 27.2% in historical controls. Cumulative incidences of death and limb amputation were only nominally lower in the lepirudin group. Bleeding events were more frequent in patients taking lepirudin than in historical control patients ($p = 0.02$).

The outcome of these two studies led the US and European regulatory authorities to approve lepirudin for anticoagulation in patients with thromboembolic disease related to HIT in order to prevent further thromboembolic complications.

Outcomes from the studies of the lepirudin-treated HIT patients were recently compared with outcomes from studies of danaparoid sodium-treated patients.[65] This comparative retrospective analysis showed that the efficacies of therapeutic doses of danaparoid or lepirudin in preventing death, amputation or new thromboembolic events in HIT patients did not differ greatly ($p = 0.02$ in favour of danaparoid sodium in patients without thromboembolic events at baseline and not significant between treatments for patients with events at baseline). The risk of bleeding was higher in lepirudin-treated patients (2.4% vs 10.4%; $p = 0.009$). However, since there are no prospective data comparing lepirudin and danaparoid sodium for treatment of HIT, a definitive conclusion on the relative efficacy and safety of these two therapeutic modalities cannot be made.[36]

2.4.3 Monitoring Treatment with Direct Thrombin Inhibitors

Because of the potential bleeding risk with administration of all thrombin inhibitors, it is important to monitor patients being treated with these agents. Tight control by laboratory monitoring is essential for efficacy and safety in all patients. Particular attention should be given to elderly patients and those with renal or liver failure. Dosage determined by monitoring may differ from generally recommended dosage. Laboratory monitoring of the antithrombin agents lepirudin and argatroban is described in detail in the manufacturers' product brochures, package inserts and in prescribing guidelines such as the Physician's Desk Reference in the US.

For lepirudin, the manufacturer recommends the use of a ratio of the aPTT test: i.e. patient's aPTT/median of the laboratory's normal range. The target ratio is 1.5–2.5. This corresponds to 1.0–1.5 μg/mL plasma concentrations.

It is recommended that argatroban be monitored by a ratio of the patient's aPTT/patient's baseline aPTT, with a target range of 1.5–3.0. This corresponds to circulating plasma concentrations of about 1.0–1.5 μg/mL. The aPTT should not be above 100 seconds according to the manufacturer's labelling.

The aPTT test is used to monitor thrombin inhibitors only because it is widely available, inexpensive and easy to perform. There are, however, several precautions when using aPTT to monitor these drugs. Specific values for the aPTT seconds of time to clot differ for each reagent/instrument system, as has been observed in some of the clinical trials[63,64] as well as by our personal observation. Therefore, the aPTT ratio is safer to use than the aPTT seconds of time to clot to eliminate the varying sensitivities of aPTT systems.

The correlation of aPTT with plasma lepirudin levels is only fair.[66,67] The aPTT is sensitive to low concentrations of lepirudin (<0.5 μg/mL) but poorly sensitive to high concentrations of lepirudin (>1.5 μg/mL). The ecarin clotting time test (ECT), on the other hand, is linearly correlated with lepirudin concentrations.[66] Thus, monitoring by the ECT is an alternative that may eventually prove to be useful, but as yet this test is not state-of-the-art in most laboratories. Reagents and the assay procedure are not readily available. It is not an FDA-approved assay.

One need also be aware that other laboratory tests using the clotting endpoint, such as fibrinogen, coagulation factor assays, the prothrombin time (PT) and other global clot-based assays, are also affected by thrombin inhibitors.[68,69] Therapeutic ranges for the PT and thrombin time tests have not been identified for argatroban or lepirudin therapy. Results from factor assays are artificially abnormal if the patient is on thrombin inhibitor treatment at time of

specimen collection.[70] Thrombin inhibitors exert no effect on vitamin K-dependent factor levels; true factor levels can be measured by chromogenically or immunologically based assays.[70]

2.4.4 Coadministration of Warfarin Derivatives and Thrombin Inhibitors

Certain patients who develop HIT require long-term anticoagulation: e.g. patients with a history of thrombosis, patients at high risk of developing thrombosis, or patients with thrombosis, pulmonary embolism, artificial heart valves or atrial fibrillation. There are special considerations for dosage of warfarin derivatives/OAC in patients during the acute phase of HIT. Of primary importance is to *not* administer warfarin alone without prior anticoagulation with a substitute drug to heparin. Because of potential low levels of protein C, as well as the slow onset of action of the OAC in the face of the heightened hypercoagulable state in HIT, the OAC is not to be used as the sole anticoagulant in patients with HIT. Similarly, loading doses of the OAC should not be given. The risk of skin necrosis/gangrene can be reduced by following these guidelines. For patients with HIT receiving thrombin inhibitor anticoagulation and requiring long-term anticoagulation, both the thrombin inhibitor and the OAC are to be used concurrently during the induction period of the OAC.

Use of warfarin derivatives should be initiated only when the patient is fully anticoagulated with a substitute drug, and then only when platelet counts are rising and above 100 000/μL. OAC therapy should be at an average standard maintenance dose of the vitamin K antagonist of choice (e.g. 5 mg/day or a lower dose for Coumadin®[1]). A loading dose is not necessary and may be hazardous. The antithrombin drug should be continued until the International Normalised Ratio (INR) is in the therapeutic range and at a safe level (see the specific product insert for manufacturer's guide). Risk factors for an excessive response to OAC (age, nutrition, hepatic disease, postoperative state, antibiotic, etc.) must be taken into account. An INR of >4.0 may result in warfarin-induced skin necrosis or limb gangrene.[20] In an 8-patient study, a median INR of 5.8 was associated with limb gangrene, whereas a median INR of 3.1 was not.[20] Duration of OAC treatment is based on the underlying medical problem.

In a study of argatroban and warfarin, it was demonstrated that concurrent use of the thrombin inhibitor and warfarin prolongs the PT/INR beyond that produced by warfarin alone.[68,69] Hence, the traditional relationship between the INR and bleeding is altered. Cotherapy INRs increase linearly with INRs on warfarin monotherapy, and the slope of this relationship is sensitive to the argatroban plasma concentration and the thromboplastin reagent used.[69]

Specifically, for cotherapy of argatroban ≤2 μg/kg/min and warfarin, argatroban can be discontinued when the cotherapy INR is 4.0. Upon cessation of argatroban, the INR should be checked 4–6 hours later, when the effect of argatroban is negligible, to ensure an actual therapeutic value reflective of warfarin monotherapy. For cotherapy of argatroban >2 μg/kg/min and warfarin, the argatroban dose should be temporarily (4–6 hours) reduced to 2 μg/kg/min, and then the guideline for cotherapy of argatroban 2 μg/kg/min and warfarin should be followed.

A similar transition guideline should be followed for the lepirudin-OAC crossover.

2.4.5 Treatment of HIT with Life-Threatening Thrombosis

Specific treatments for thromboembolic complications should be immediately carried out in conjunction with medical antithrombotic therapy if it is probable that argatroban or lepirudin are not going to be capable of preventing serious organ or tissue damage or death. Consultations with surgical specialists and interventionists should be requested on an emergency basis to reduce the risks associated with these procedures.

Extraction of thrombi by surgical means has well established indications and methods, whereas thrombolytic therapy is less well established. Many interventional cardiologists and radiologists are

1 Use of tradenames is for product identification only and does not imply endorsement.

competent at performing these procedures, as are some vascular surgeons. An expert may have to be urgently sought from a tertiary-care centre if one is not locally available. Pulmonary embolism is a particularly serious emergency.[71]

Thrombolytic therapy for pulmonary embolism, venous thrombosis, and coronary and peripheral arterial thrombosis has been reported for the management of HIT.[72-76] General consideration regarding the current use of thrombolytic therapy is set forth in consensus documents of 1996[77] and 1998.[78] Urokinase has recently been taken off the market because of suspected contaminants in the product. This may eventually be resolved. The 1998 recommendations are likely to be updated by periodic working party publications.

Thrombolytic therapy is usually administered systemically for coronary artery occlusion, resulting in a risk of haemorrhage in high-risk patients such as those who may have had recent surgery or a stroke. The risk-benefit ratio must be carefully assessed in such patients and alternative therapy considered if the risk of haemorrhage is high. Local infusion of thrombolytic agents generally has a lesser risk, but careful monitoring for a systemic effect using the thrombin time and fibrinogen levels as well as platelet counts is advisable. A haematology consultation should be sought. Combined use of direct thrombin inhibitors and thrombolytic agents constitutes a very high risk for haemorrhage and is not recommended.

2.4.6 Percutaneous Coronary Interventions in HIT Patients

Several multicentre, prospective, open-label studies (ARG-216, ARG-310, ARG-311) evaluated argatroban for anticoagulation in HIT patients undergoing percutaneous coronary intervention (PCI).[79,80] Procedures included percutaneous transluminal coronary angioplasty (PTCA), stent implantation or rotational atherectomy. Argatroban was administered at 25 μg/kg/min infusion (350 μg/kg initial bolus dose) adjusted to achieve an activated clotting time (ACT) of 300–450 seconds during the procedure. Additional bolus doses of 150 μg/kg to achieve or maintain the target ACT were allowed but usually unnecessary. Target ACT values were achieved typically within 10 minutes of initiation of argatroban.

Primary efficacy assessments were subjective assessments of the satisfactory outcome of the procedure and adequate anticoagulation, which occurred in 94.5 and 97.8%, respectively, of patients undergoing their initial PCI with argatroban (n = 91). One patient required emergency coronary artery bypass surgery, and one patient experienced major periprocedural bleeding. No unsatisfactory outcomes occurred during repeat PCIs with argatroban (n = 21). Overall, the clinical outcomes compared favourably with those reported historically for heparin anticoagulation during PCI.

The US FDA has approved the use of argatroban for anticoagulation of HIT patients during PCI.

2.4.7 Cardiac Surgery with Thrombin Inhibitors

Perhaps the greatest obstacle to overcome in the management of patients with HIT antibody is anticoagulation during surgical coronary revascularisation. Consultation from experts is strongly advised for any patient with HIT requiring cardiac surgery.

It has been suggested that a brief exposure to heparin could be considered under compelling circumstances for patients with a history of HIT who have HIT antibodies undetectable by a functional platelet assay. In this situation, heparin exposure should be restricted to the surgical procedure, with alternative anticoagulation used for postoperative antithrombotic prophylaxis or therapy. Standard heparin protocols restricted to the surgery itself can be used, but only after antibody titres are allowed to decrease and laboratory tests give negative results.[22,81,82] Postoperative anticoagulation should be with a direct thrombin inhibitor and/or a warfarin derivative, not heparin or a LMWH. Performing surgery with a combination of heparin and an antiplatelet agent such as tirofiban or iloprost has been reported but this regimen has not been validated.[83]

The use of lepirudin as an anticoagulant during cardiopulmonary bypass surgery (coronary artery grafting, aortic valve replacement) in patients with HIT has been described in a number of small studies and case reports.[84-86] While large-scale trials to

identify the optimal dosage of lepirudin have not been performed, it appears that clotting can be avoided at lepirudin concentrations of about 3–5 μg/mL (bolus of 0.25 mg/kg, 0.2 mg/kg in the priming fluid, 0.5 mg/min intravenous infusion). Patients with renal impairment have an increased risk of postoperative bleeding because of the decreased rate of elimination of lepirudin[51,87] Isolated cases using lepirudin anticoagulation for cardiac surgeries without the cardiopulmonary bypass pump (left ventricular assist device, off-pump) are also being reported.[88,89] A lower dose of lepirudin is used in these cases.

Monitoring such high levels of lepirudin that are required for cardiac surgery is another unresolved issue. The ACT is not appropriate, since it is too sensitive, but it may be possible to use the ECT.[66,88] The ECT, however, has not been standardised and is not widely available. Another possibility is a plasma-modified ACT described by one group.[90]

2.4.8 Other Clinical Uses of Thrombin Inhibitors in HIT Patients

Case reports describe the successful use of argatroban anticoagulation in patients with HIT during renal stent implant and carotid stent implant.[91,92] The argatroban dosage was similar to that described for coronary interventional procedures. Case reports describing the successful use of argatroban and lepirudin anticoagulation during haemodialysis in HIT patients have also been published.[93-97]

2.5 Other Reported Treatment Modalities

Less commonly used therapeutic measures for patients with HIT include plasmapheresis,[98] intravenous gammaglobulin[99] and aspirin. Aspirin is usually started only after thrombocytopenia has resolved to a platelet level of at least 100 000/μL. These modalities may very well be effective in some patients but no clinical trials have been conducted to assess their benefit and risk in HIT.

2.6 Newer Therapies

Bivalirudin is a synthetic, direct thrombin inhibitor with a lower molecular weight than hirudin. It consists of two small peptide sequences that bind directly to the active site and the exosite of thrombin. It is a reversible inhibitor of thrombin. Although it is largely renally excreted, bivalirudin can be used in both renally and hepatically impaired patients with dose adjustment. It is currently in phase II clinical development for anticoagulation in HIT patients.[100,101] Bivalirudin has US FDA approval for use in PTCA, although this is for non-HIT patients.

Factor Xa inhibitors such as the synthetic pentasaccharide fondaparinux sodium[102] may prove to be useful, since there is no cross-reactivity with heparin antibodies.[48,103] Orally active antiplatelet and anticoagulant drugs currently being developed may eventually prove useful as well.

Despite the potent anticoagulant effect of direct thrombin inhibitors demonstrated in the clinical trials, there remains an unacceptable level of thrombosis-related morbidity and mortality in HIT patients. *In vitro* studies demonstrate that thrombin inhibitors are not effective at suppressing platelet activation induced by heparin antibody/heparin, whereas glycoprotein (GP) IIb/IIIa and ADP platelet receptor inhibitors are effective.[104-106] This includes inhibition of the formation of platelet microparticles, which are thought to generate the procoagulant state in HIT patients. This concept has been supported by limited clinical experience. Patients who had limb-threatening thrombi resistant to thrombin inhibitor treatment responded favourably to a standard dose of a GPIIb/IIIa inhibitor administered with a reduced dose of a thrombin inhibitor.[106] Although this treatment is promising, optimal dosage regimens have not yet been established.

3. Pregnancy and HIT

In pregnancy, patients with mechanical prosthetic heart valves are often treated with heparin because of the risk of embryopathy with warfarin derivatives, especially during weeks 6–12. If HIT should occur, there is no proven effective prophylaxis for thromboembolism arising from the valve other than warfarin. Some experts advise warfarin throughout pregnancy in these patients whether they have HIT or not, based on the belief that heparin therapy is not as effective in preventing thromboem-

bolism as is warfarin.[107-110] Such difficult decisions should be made in consultation with the patient and her partner as well as with haematologists and obstetricians.

If the pregnant patient with HIT has need for continuous anticoagulation for an indication other than for a mechanical heart valve, warfarin is probably the best choice. A LMWH would, in this instance, also be a choice to consider provided *in vitro* testing by SRA with heparin is positive but is negative with the LMWH.[40] Continuous monitoring of clinical findings, platelet counts and evidence for seroconversion would be advisable here. A LMWH in these circumstances could pose a significant risk for the pregnant patient in terms of potential bleeding at time of delivery; however, warfarin would be more hazardous than a LMWH for the fetus.[110] In such cases the pregnant patient should be a part of therapeutic decision making.

The use of thrombin inhibitors in the pregnant patient is uncertain. Lepirudin crosses the placenta to some extent and argatroban is untested in pregnancy. However, because of lack of another alternative, there have been several cases where lepirudin was used to treat venous thrombosis due to HIT in pregnant women. Treatment with 15mg subcutaneous lepirudin twice daily from the 25th week was reported to be successful with no fetal toxicity or bleeding.[111,112]

4. Conclusions

The key to successful management of HIT is careful monitoring for thrombocytopenia and thrombosis during, and for at least several days after, heparin therapy of any duration. Suspicion of the diagnosis based on clinical information should lead to immediate cessation of all heparin use in the patient and to institution of alternative anticoagulant therapy. Treatment of thrombosis is critical and should be initiated as soon as possible to reduce complications. Prophylactic administration is highly recommended because of the high risk of developing thrombosis without treatment.

The current treatment of choice for HIT-associated thrombosis is a thrombin inhibitor. Argatroban and lepirudin have been proven to be safe and effective in multicentre clinical trials, and both drugs are approved for use in patients with HIT by regulatory authorities (lepirudin is approved in the US, Canada and Europe and argatroban is approved in the US and Canada [file being submitted in Europe]). Argatroban has also been approved for use in invasive cardiology procedures in the HIT patient. These drugs are potent anticoagulants and need to be used with care according to accepted dosage regimens to avoid bleeding. Off-label use, such as in cardiac surgery, must be approached with extreme caution until dosage regimens and monitoring assays are established.

Other treatment options for the patient with HIT include dextran, plasmapheresis, intravenous gammaglobulin and antiplatelet drugs. Although these modalities may be effective, they have not been rigorously tested. In extreme circumstances where there is life- and limb-threatening thrombosis, thrombolytic agents and/or surgery may provide benefit; however, these procedures have a high risk of failure if performed by the inexperienced.

Patients with HIT requiring continued anticoagulation should be given a warfarin derivative in accordance with the stated recommendations (i.e. under prior anticoagulation with a thrombin inhibitor, special considerations of the effect of the drug combination on the INR, etc.). Subsequent use of heparin or a LMWH after resolution of the clinical episode of HIT can be hazardous, particularly in the first 3 months after diagnosis of HIT. If needed, laboratory testing is advised. If the result is negative, heparin may be cautiously reinstituted for short-term use (1–2 hours) with monitoring for unusual fall in platelet counts or thromboembolism.

Although today there are realistic treatment options for the patient with HIT, the morbidity and mortality associated with this disease have not been eliminated. New therapeutic modalities continue to be considered for use in this patient population. Perhaps the most valuable recent observation is that the new antiplatelet drugs (not thrombin inhibitors) target the platelet activation that occurs in HIT. In the future, prophylaxis and treatment of HIT throm-

bosis may incorporate the use of multiple drugs: for example, thrombin inhibitors to target coagulation coupled with GPIIb/IIIa inhibitors to target activated platelets.

The risk of thrombosis is very high in HIT patients who are untreated. On the other hand, the benefit of antithrombotic treatment is obvious. Yet there is a risk of bleeding with any antithrombotic drug, and protection against thrombosis is not always complete. Despite these limitations, the current treatments for patients with HIT provide unparalleled benefit compared with the treatment options available only a few years ago.

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