HIT/HITT and alternative anticoagulation: current concepts

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Heparin is a widely used anticoagulant for the treatment and prevention of thromboembolic disorders in medical and surgical patients. Its importance as an anticoagulant has been well established by its effectiveness, rapid onset of action, ease of laboratory monitoring and cost. Heparin is a member of the heterogeneous family of glycosaminoglycans, which range in size from 3000 to 30 000 Da. The non-branching, negatively charged chain structure of heparin consists of repeating disaccharide units. Heparin is an anticoagulant released by mast cells and basophils in the process of clot formation, as well as a drug that is administered to the same effect. Standard unfractioned heparin is usually derived from porcine intestinal mucosa or bovine lung.

Heparin plays many roles in human physiology, such as: (i) binding to antithrombin III and increasing the efficacy of antithrombin III as an inhibitor of the activation of thrombin and certain clotting factors; (ii) inhibiting platelet formation; (iii) increasing the permeability of vessel walls; (iv) inhibiting the proliferation of vascular smooth muscle cells; and (v) playing a role in the regulation of angiogenesis.

In clinical use heparin has numerous activities, but the most important is its anticoagulant property (Table 1). It is also used as a thrombolytic, a fat-clearing anti-atherosclerotic and as a potentially effective anti-inflammatory agent. Heparin inhibits reactions that lead to clotting of blood and formation of fibrin clots both in vitro and in vivo. It acts at multiple sites in the normal coagulation system. It binds to antithrombin III (heparin cofactor), causing a conformational change in the structure of antithrombin III. This conformational change converts antithrombin III from a slow- to a fast-acting inhibitor of thrombin activation. The complex has a further inhibitory effect on other clotting factors, such as factors IX, X, XI and XII and kallikrein, and on the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin-stabilizing factor.

Thrombocytopenia and heparin

Thrombocytopenia can result from conditions that lead to increased platelet destruction or decreased platelet production (Table 2). Heparin can cause thrombocytopenia via immune and non-immune mediated mechanisms. There are two types of heparin-induced thrombocytopenia that can result from heparin administration: type I, non-immune-mediated; and type II, immune-mediated. In the interest of standardization, the term ‘non-immune heparin-associated thrombocytopenia’ is recommended for type I, a benign condition in which no heparin-dependent antibodies are present. The term ‘heparin-induced thrombocytopenia’ (HIT) is recommended for thrombocytopenia in which pathogenic heparin-dependent antibodies are detectable. This term is the most widely accepted designation for HIT type II.

Non-immune-mediated thrombocytopenia, also known as heparin-associated thrombocytopenia (HAT) and heparin-induced thrombocytopenia type I (HIT type I), denotes the absence of heparin-dependent antibodies. It is probably caused by direct non-immune platelet activation by heparin. Type I HIT is usually associated with larger doses of heparin in contrast to HIT type II, which can occur with variable doses. HIT type I occurs earlier in the treatment course,
within a period of 4 days, in 30% of patients receiving heparin. The platelet abnormality is usually mild and reversible even with the continuation of the heparin (Table 3). The condition is self-limiting and there are no major complications associated with it. Heparin should be continued despite the low platelet count. The clinical importance of the asymptomatic, self-limiting disease HIT type I lies in the necessity of differentiating it from the more serious HIT type II.

**Immune-mediated HIT type II** exists in three separate diagnosable forms:

(i) latent: antibodies without thrombocytopenia;
(ii) HIT: antibodies with thrombocytopenia; and
(iii) HITT: antibodies with thrombocytopenia and thrombosis.

**HIT/HITT** (heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis syndrome) is an immune-mediated adverse reaction to heparin that is often underdiagnosed and can result in venous and arterial thrombosis. The alternative name of HITT, white clot syndrome, refers to the gross pathology of the clots. The platelet–platelet adhesion without erythrocyte involvement gives a classic appearance of a white clot. Patients with HITT may suffer from venous thrombosis, most often deep venous thrombosis (DVT), which can be extensive and complicated by pulmonary embolism. Venous limb gangrene has been reported to occur with warfarin treatment of HIT-associated DVT, and is characterized by a high international normalized ratio (INR), resulting from severe reduction in protein C caused by warfarin. Adrenal vein thrombosis and cerebral sinus thrombosis are other unusual venous thromboses that complicate HIT. Arterial thromboses associated with HITT may result in ischaemic limb damage that often requires amputation. Myocardial infarction, ischaemic stroke and end-organ thromboses, such as mesenteric, renal, brachial, splenic and hepatic arterial thromboses, can also occur (Table 4).

**Mechanism of heparin–PF4–IgG complex**

Most patients with HIT produce immunoglobulin G (IgG) antibodies, commonly IgG1 against macromolecular complexes of platelet factor 4 (PF4) and heparin (H–PF4). The high binding affinity between heparin and PF4 is probably attributable to a high concentration of C-terminus lysine residues that interact strongly with the heparin.

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**Table 1 Clinical uses of heparin**

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Acute-phase myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous and arterial thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
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<tr>
<td></td>
<td>Atrial fibrillation with embolization</td>
</tr>
<tr>
<td></td>
<td>Acute ischaemic stroke</td>
</tr>
<tr>
<td></td>
<td>Deep vein phlebitis</td>
</tr>
<tr>
<td>Topical</td>
<td>Flap survival/pruritus</td>
</tr>
<tr>
<td></td>
<td>Leg ulcers</td>
</tr>
<tr>
<td>Surgery</td>
<td>Open-heart surgery</td>
</tr>
<tr>
<td></td>
<td>Vitreoretinal surgery</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Support systems</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>Critical care</td>
<td>Extracorporeal circulation</td>
</tr>
<tr>
<td></td>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>Critical care</td>
<td>Heparin-coated central venous and pulmonary arterial catheters</td>
</tr>
<tr>
<td>Critical care</td>
<td>Heparin flushes in arterial and central venous lines</td>
</tr>
<tr>
<td>Other (as anticoagulant)</td>
<td>Laboratory samples</td>
</tr>
<tr>
<td></td>
<td>Blood transfusion</td>
</tr>
</tbody>
</table>

**Table 2 Causes of thrombocytopenia**

<table>
<thead>
<tr>
<th>Increased platelet destruction</th>
<th>Septicaemia/inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-immune</td>
<td>Disseminated intravascular coagulation (DIC)</td>
</tr>
<tr>
<td></td>
<td>Thrombotic thrombocytopenia purpura (TTP)</td>
</tr>
<tr>
<td>Immune</td>
<td>Autoimmune: idiopathic or secondary immune thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Allotimmune: post-transfusion purpura</td>
</tr>
<tr>
<td></td>
<td>Drug-induced: prothrombic (heparin), prohaemorrhagic (quinine, quinidine, gold, sulpha antibiotics, rifampicin, vancomycin, NSAIDs)</td>
</tr>
<tr>
<td>Decreased platelet production</td>
<td>Alcohol, cytotoxic drugs</td>
</tr>
<tr>
<td>Alcohol, cytotoxic drugs</td>
<td>Leukaemia, aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td>Myelodyplasia</td>
</tr>
<tr>
<td></td>
<td>Metastatic bone marrow involvement</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
</tr>
<tr>
<td>Other causes</td>
<td>Hypersplenism</td>
</tr>
<tr>
<td></td>
<td>Haemodilution (infusion of blood products, colloids, crystalloids)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs=non-steroidal anti-inflammatory drugs.</td>
</tr>
</tbody>
</table>

**Table 3 Heparin-induced thrombocytopenia**

<table>
<thead>
<tr>
<th>Onset</th>
<th>Within 4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Typically 100 000–150 000 μl⁻¹</td>
</tr>
<tr>
<td>Incidence</td>
<td>5–30%</td>
</tr>
<tr>
<td>Complications</td>
<td>None</td>
</tr>
<tr>
<td>Recovery</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Cause</td>
<td>Benign: tiny platelet aggregates</td>
</tr>
</tbody>
</table>

**Non-immune-mediated HAT (type I HIT)**

<table>
<thead>
<tr>
<th>Onset</th>
<th>Within 4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Typically 100 000–150 000 μl⁻¹</td>
</tr>
<tr>
<td>Incidence</td>
<td>5–30%</td>
</tr>
<tr>
<td>Complications</td>
<td>None</td>
</tr>
<tr>
<td>Recovery</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Cause</td>
<td>Benign: tiny platelet aggregates</td>
</tr>
</tbody>
</table>

**Immune-mediated HIT (type II HIT)**

<table>
<thead>
<tr>
<th>Onset</th>
<th>5–14 days or sooner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Typically 20 000–150 000 μl⁻¹</td>
</tr>
<tr>
<td>Incidence</td>
<td>1–3%</td>
</tr>
<tr>
<td>Complications</td>
<td>Thromboembolic lesion</td>
</tr>
<tr>
<td>Recovery</td>
<td>5–7 days</td>
</tr>
<tr>
<td>Cause</td>
<td>IgG-mediated platelet activation</td>
</tr>
</tbody>
</table>
with the highly negatively charged heparin molecule. Neither heparin nor PF4 is normally antigenic, but the formation of an H±PF4 complex induces a conformational change in both molecules. Upon binding to the heparin molecule, PF4 exposes several antigenic epitopes, which trigger the immune reaction and the production of immunoglobulin G. These antibodies activate platelets through their FcRIIA receptors, causing platelet destruction and release of prothrombotic platelet-derived microparticles. Micro-particles in turn promote thrombin generation and contribute to a hypercoagulable state (Fig. 1). PF4, a small peptide stored within the alpha granules of platelets, binds to heparin and is released into the blood during treatment with it. In vitro, IgG±PF4±heparin complexes can activate platelets. Increased propensity to thrombosis in HIT is therefore probably mediated by thrombin generated as a result of in vivo platelet activation, from interaction between heparin–PF4–IgG immune complexes with Fc receptors on platelets. A minimum of 12–14 saccharides is required to form the antigenic complex with PF4. Heparin molecules with a molecular weight >4000 Da have the potential to cause HIT. Hence HIT is less common with low molecular weight heparin (LMWH) than with unfractioned heparin. No specific laboratory or clinical characteristics can predict which patients will have isolated thrombocytopenia or have thrombocytopenia with thrombotic complications.

**Diagnosis of HIT**

Manifestations of HIT include an otherwise unexplained decrease in platelet count and skin lesions at heparin injection sites, accompanied by HIT antibody formation. The platelet count during HIT can be variable, but only rarely decreases to <20 000×10⁹ litre⁻¹. The median platelet count nadir in several studies is ~50 000×10⁹ litre⁻¹. HIT should also be suspected if the platelet count decreases by 30–50% after 5 days of heparin treatment (Table 3). The occurrence of thromboembolic complications during heparin therapy is another strong marker of HIT. Regardless of the degree of thrombocytopenia, the predominant clinical feature is thrombosis and not bleeding. The decrease in platelet count almost always occurs between days 5 and 15 after the introduction of heparin, but can develop earlier in patients exposed to heparin during the previous 3 months. Case reports have shown thrombocytopenia developing within 10.5 h in patients exposed to heparin in the last 100 days. Thus, a patient with a rapid decrease in platelets soon after commencing heparin therapy, who has not been exposed to heparin previously, probably has another aetiology for the thrombocytopenia. During recovery from thrombocytopenia, heparin-dependent antibodies in the serum decrease to undetectable levels by 50–85 days. Those with undetectable antibody but a previous proven diagnosis of HIT type II may take as long as 5 days to produce IgG antibodies and thrombocytopenia.

**Laboratory diagnosis**

There are two main classes of assays for laboratory diagnosis of HIT. Activation (functional) assays include the platelet aggregation assay and the serotonin release assay. The platelet aggregation assay involves the use of washed platelets rather than platelet-rich plasma derived from normal donors. This increases the reliability of activation assays, which are performed in the laboratory.
with a specificity >90%. The disadvantages are low sensitivity (35%) and the fact that assay reactivity varies between donor platelets. The serotonin release assay measures the release of serotonin from platelet aggregates. It relies on the aggregation of the platelets from the patient in the presence of heparin. This assay has high sensitivity and specificity and has been validated by blinded assessment of clinical trials. The disadvantages are that the assay is technically demanding and involves the use of radioactive materials. Of the various activation assays available, those that use washed platelets and platelet serotonin release or heparin-induced platelet activation (HIPA) are the most accurate.

The other class of assay is the antigen assay. The heparin–PF4 enzyme-linked immunosorbent assay (ELISA) relies on the specificity of HIT IgG antibodies for the heparin–PF4 complex. This assay is 10 times more sensitive than the serotonin release assay for detecting heparin-induced antibodies. However, the heparin–PF4 ELISA is expensive and time-consuming. The assay also responds to clinically insignificant antibodies more often than activation assays, and hence has a lower specificity.

Most of the available laboratory tests for the diagnosis of HIT are expensive, time-consuming, frequently contradictory to the clinical presentation, and vary in sensitivity and specificity. Testing a patient with a history of HIT before expected heparin re-exposure should therefore be done with more than one sensitive test. Hence, the diagnosis of HIT remains clinical. It should be suspected in patients who develop thrombocytopenia with or without associated arterial or venous thrombosis while on heparin.

Prevention of HIT

Currently there are no tests available to predict which patients are at high risk of developing HIT. Therefore, whenever heparin is clinically indicated, it is necessary to assess the risk–benefit profile in all patients. The following points should be considered in the prevention of HIT:

(i) history of previous sensitization to heparin—requires initiation of alternative anticoagulant therapy;
(ii) limit heparin duration to less than 5 days whenever possible;
(iii) early use of warfarin in patients requiring long-term anticoagulation, except when HIT is diagnosed;
(iv) initiating warfarin at the start of heparin treatment in patients who require long-term anticoagulation;
(v) use of LMWH—a prospective study shows LMWH is less likely to cause HIT and HIT–IgG antibodies;
(vi) avoid unnecessary heparin flushes;
(vii) use of porcine heparin (frequency of HIT, 1.3–8%) rather than bovine heparin (frequency of HIT, 1.9–30.8%);
(viii) regular monitoring of platelet count.

Management of HIT

After the clinical diagnosis or suspicion of HIT, heparin should be discontinued promptly. The platelet count should be monitored carefully and warfarin should not be used alone in patients with acute HIT. Management of the patient with HIT is aimed at prevention of the thromboembolic complications seen in 50–70% of patients. The mortality associated with isolated thrombocytopenia without thrombosis is 21%. Therefore, the principle of managing HIT is the discontinuation of all forms of heparin exposure and the institution of an alternative anticoagulant. The diagnosis should be confirmed as soon as practicable, but treatment should not be delayed for this reason. In the absence of thrombosis, cessation of heparin has been the traditional mode of therapy, but several studies have shown that stopping heparin may be inadequate because of the high risk of overt thrombosis (50%) in the week after its interruption.

Warfarin in HIT

Warfarin should not be used alone to treat acute HIT complicated by DVT because of the paradoxical risk of developing venous limb gangrene, which causes more than half the limb loss attributable to HIT at one centre. Rapid loading with warfarin can cause depletion of the anticoagulant vitamin K-dependent protein C faster than it depletes procoagulant vitamin K-dependent proteins. Higher warfarin doses cause a rapid increase in the INR, but this is entirely a result of earlier reduction of factor VII rather than a reduction in factor II, a coagulable protein with a longer half-life. Initiating warfarin therapy with a relatively high loading dose for rapid anticoagulation, which is a common practice, may prove dangerous, particularly in HIT. Although other thrombin inhibitors have been introduced for continuing anticoagulation in the place of heparin, warfarin still remains an option for patients with HIT who require anticoagulation. Studies have shown that aiming for modest levels of the INR with warfarin and a smaller loading dose prevents the development of a potential hypercoagulable state caused by a precipitous decrease in the concentration of protein C.

It is therefore important to start treatment in all patients with HIT who remain at risk of thrombosis, including postoperative patients and those with sepsis. Thrombin inhibitors (lepirudin or argatroban) should be used in these patients until the platelet count has recovered. Treatment with thrombin inhibitors should also be considered for patients with acute HIT without thrombosis (isolated HIT), because there is a high risk of subsequent clinically evident thrombosis. Warfarin given to patients adequately anticoagulated with lepirudin appears safe in acute HIT, but it is prudent to delay starting warfarin until the platelet count has risen above 100×10^9 litre^-1.
Low molecular weight heparin and HIT

Low molecular weight heparin does not bind strongly to plasma proteins and endothelial cells; its bioavailability is much greater than with unfractionated heparin and there is also a more predictable dose response. However, low molecular weight heparins have a high in vitro cross-reactivity rate with heparin-dependent antibodies, reaching 100% in some very sensitive assays. Low molecular weight heparins can cause HIT, and when used in its treatment there is a significant risk of recurrent or progressive thrombocytopenia with or without thrombosis. Because of these drawbacks, and as there are other effective drugs available, low molecular weight heparins are not recommended for the management of patients with HIT.

Danaparoid in HIT

Danaparoid sodium (Orgaran®) does not contain heparin and is a low molecular weight heparinoid. It is a mix of dermatan sulphate, glycosaminoglycans and chondroitin sulphate. The use of danaparoid is associated with a favourable outcome in 90% of patients with HIT. The main activity of danaparoid is against factor Xa, with the anti-Xa:anti-IIa ratio of 22:1 resulting in inhibition of fibrin formation. The potential disadvantage is the prolonged half-life of anti-factor Xa activity (around 25 h). This is disadvantageous for patients who are at risk of bleeding and who might need a surgical procedure. There is a 10–20% cross-reactivity rate with HIT antibodies in vitro, although it is less common in vivo. Danaparoid does not interfere with INR measurements, and therefore allows concurrent and easy monitoring of warfarin anticoagulation.

Prostacyclin analogues in HIT

Prostacyclin is a natural vasodilator and inhibitor of platelet aggregation. Iloprost has been shown to be effective in suppressing HIT-induced platelet aggregation and in preventing thrombotic complications. Prostacyclin analogues have a short half-life of 15–30 min and have been preferred in cardiac and vascular surgery for anticoagulant coverage in patients with HIT. They are also used in intensive care units for anticoagulation during renal replacement therapy. The main side-effects are hypotension and bradycardia.

Thrombin inhibitors in HIT

Thrombin plays a central role in HIT-related thromboembolic complications (Fig. 2). Thrombin generation is enhanced in HIT by the concomitant activation of platelets, the generation of platelet microparticles and the alteration of endothelial cells. Thrombin inhibitors such as lepirudin and argatroban have found a greater role in the management of HIT/HITT.

Thrombin inhibitors currently available for the management of HIT and HITT are:

(i) lepirudin (Refludan®);
(ii) argatroban (Argatroban®, Novastan®);
(iii) hirulog and bivalirudin (Angiomax®) and
(iv) desirudin (ReVase®).

Lepirudin is currently licensed for the treatment of HIT/HITT in the UK, the USA and Europe. Argatroban has recently been approved for use in the prophylaxis and treatment of thrombosis in HIT in the USA and Canada. Bivalirudin and desirudin are currently not licensed for use in HIT/HITT, although their use in the treatment of this condition has been reported.

Hirudin is a direct inhibitor of thrombin and acts independently of cofactors such as antithrombin. Unlike heparin, hirudin is not inactivated by PF4 and may be more effective in the presence of platelet-rich thrombi. Hirudin can also inhibit thrombin bound to fibrin or fibrin degradation products.

Lepirudin (Refludan®) is a recombinant hirudin derived from yeast cells and is a highly specific direct and irreversible inhibitor of thrombin. One molecule of lepirudin binds with one molecule of thrombin. The half-life for distribution and elimination is 10 min and 1.3 h respectively. Lepirudin is almost exclusively excreted in the kidneys and hence systemic clearance of lepirudin is...
dependent on the glomerular filtration rate. It should therefore be used cautiously in patients with chronic renal failure and should be avoided in patients with acute renal failure (Table 5). There is an increased risk of bleeding with other anticoagulants, thrombolytics and antiplatelet drugs.

The usual adult dose is 0.4 mg kg⁻¹ bolus i.v. followed by infusion of 0.15 mg kg⁻¹ h⁻¹. Dose adjustment required in renal insufficiency (Table 5). However, the dose should not exceed an infusion rate of 0.21 mg kg⁻¹ h⁻¹ without checking for coagulation abnormalities. In haemodialysis patients and patients with acute renal failure with creatinine clearance <15 ml min⁻¹ (normally 120 ml min⁻¹) or serum creatinine >528 μmol litre⁻¹, the drug should be avoided. The infusion rate should be adjusted in patients with renal impairment (Table 6).

Ecarin clotting time (ECT) is a suitable assay for bedside real-time monitoring of lepirudin anticoagulation. Ecarin is a metalloproteinase from snake venom (Echis carinatum) that activates prothrombin to meizothrombin. Hirudin forms a 1:1 complex with meizothrombin, thus preventing the conversion of fibrinogen to fibrin and the formation of thrombin. Therefore, the clotting time is prolonged with increasing amounts of hirudin. The precision of the ECT assay is directly related to the prothrombin and fibrinogen concentration, but does not seem to be affected by the presence of heparin or oral anticoagulants. The specificity of the ECT-determined lepirudin concentration is not influenced by treatment with oral anticoagulants. The Ecarin clotting time values showed good correlation with plasma concentrations of lepirudin. In these reports, an ECT of 350–400 s corresponds to lepirudin concentrations of 3.5–4 μg ml⁻¹.

The Heparin-Associated Thrombocytopenia Trials (HAT-1 and HAT-2)²⁴ ²⁵ are prospective clinical trials of lepirudin. The clinical outcomes of patients were compared with those of a historical control group. A meta-analysis of these trial results²⁹ represents the largest population of patients with HIT and thromboembolic complications treated with lepirudin. Overall, 198 patients (82 in HAT-1, 116 in HAT-2) were treated with lepirudin and 182 historical control patients were given other treatments. All except five (one in HAT-1, four in HAT-2 group) prospective patients and all historical control patients were diagnosed with HIT using the heparin-induced platelet activation assay or equivalent assays for testing. In total, 113 (54 in HAT-1, 59 in HAT-2) prospective patients (lepirudin) and 91 historical control patients presented with thromboembolic complications at baseline (day of positive test result) and qualified for direct comparison of clinical endpoints.

In the meta-analysis, the pooled lepirudin patients of the HAT-1 and HAT-2 studies who presented with thromboembolic complications at baseline were compared with the respective historical control patients. Seven and 35 days after the start of treatment, the cumulative risks of death

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### Table 5 Comparison between lepirudin and argatroban⁷

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Lepirudin</th>
<th>Argatroban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>Direct thrombin inhibitor</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td></td>
<td>Irreversible inhibition</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Monitoring</td>
<td>aPTT, ecarin clotting time</td>
<td>aPTT</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>40–120</td>
<td>24–50</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Table 6 Dosing adjustment for lepirudin⁷

<table>
<thead>
<tr>
<th>Creatinine clearance (ml min⁻¹)</th>
<th>Serum creatinine concentration (mmol litre⁻¹)</th>
<th>Adjusted infusion rate (% of standard initial infusion rate)</th>
<th>Adjusted infusion rate (mg kg⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–60</td>
<td>140–176</td>
<td>50%</td>
<td>0.075</td>
</tr>
<tr>
<td>30–44</td>
<td>176.1–264</td>
<td>30%</td>
<td>0.045</td>
</tr>
<tr>
<td>15–29</td>
<td>264.1–528</td>
<td>15%</td>
<td>0.0225</td>
</tr>
<tr>
<td>&lt;15</td>
<td>&gt;528</td>
<td>Avoid or stop infusion</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis patients</td>
<td></td>
<td>Give 0.1 mg kg⁻¹ every other day only if the aPTT falls below the lower therapeutic limit of 1.5</td>
<td></td>
</tr>
</tbody>
</table>
were 4.4 and 8.9% respectively in the lepirudin group, compared with 1.4 and 17.6% in the historical control group. The cumulative risks of limb amputation were 2.7 and 6.5% in the lepirudin group compared with 2.6 and 10.4% in the historical control group. Most importantly, the cumulative risks of new thromboembolic complications were 6.3 and 10.1% in the lepirudin group and 22.2 and 27.2% in the historical control group. The differences in the cumulative risk of death, limb amputation or new thromboembolic complications between the groups were statistically significant in favour of lepirudin in the analysis of time to event (P=0.004).

***Bivalirudin*** (Angiomax®) is a direct thrombin inhibitor and an analogue of the peptide fragment hirugen, a compound derived from hirudin. Unlike lepirudin, the binding of bivalirudin to thrombin is reversible. Bivalirudin binds specifically to the catalytic site and substrate-binding site of thrombin. Bivalirudin has been approved by the US Food and Drug Administration (FDA) for use in patients undergoing coronary angioplasty with unstable angina who are also on aspirin therapy.

**Argatroban** (Argatroban®, Novastan®) is a direct competitive synthetic inhibitor of thrombin derived from L-arginine, with a molecular weight of 526. It binds reversibly to the thrombin catalytic site and thus inhibits reactions that are catalysed or induced by the presence of soluble and clot-bound thrombin. Actions inhibited by the presence of argatroban include fibrin formation and activation of coagulation factors V, VIII and XIII and the natural anticoagulant protein C.34 51 61 It is 100% bioavailable when given i.v. and is metabolized in the liver by cytochrome P450 enzymes. Unchanged drug is excreted in the urine (22%) and faeces (14%). The primary metabolite exerts an anticoagulant effect that is three to five times less potent than that of the parent drug. It is eliminated as its metabolite in the faeces (65%), presumably through biliary secretion, and in the urine (22%). Argatroban is contraindicated in patients with active bleeding or known hypersensitivity to the agent. Bleeding is the major adverse effect of argatroban, occurring in 2.3–14.4% of patients in clinical trials. The effective dose is titrated against the aPTT and activated clotting time (ACT). The drug has a predictable pharmacokinetic and pharmacodynamic profile, and there is dose-dependent response in aPTT and ACT.

Argatroban is given as an initial bolus of 2 μg kg⁻¹ min⁻¹ in adult patients without hepatic impairment. The infusion rate is titrated according to the desired level of anticoagulation. An aPTT ratio of 1.5–3.0 is usually achieved within 4 h of i.v. administration.

A study with argatroban enrolled 304 patients into two arms—160 patients in the HIT arm and 144 in the HITT arm (Table 7). They were compared with 193 historical control subjects with HIT (n=147) or HITT (n=46).44 Outcomes of these patients were compared with those of the historical controls for a period of 37 days after administration of argatroban in the treatment group and after diagnosis of HIT or HITT in the control group. The primary efficacy end-point was a composite of all-cause death, all-cause amputation and new thrombosis within 37 days of baseline. The secondary efficacy end-point included the individual components of the composite end-point together with death caused by thrombosis, any new thrombosis, achievement of adequate anticoagulation, and resolution of thrombocytopenia. Argatroban was initiated at 2 μg kg⁻¹ min⁻¹ and titrated to maintain aPTT at 1.5–3 times baseline for 14 days. Treatment continued for an average of 5.3 days in the HIT group and 5.9 days in the HITT group. In patients with HIT, argatroban therapy significantly reduced new thrombosis when compared with control subjects (8.1 vs 22.4%, P<0.001). However, the reduction in new thromboses in patients with HITT on argatroban therapy was more modest when compared with the reduction in the controls (19.4 vs 34.8%, P=0.044). There was no decrease in death or amputation caused by all causes in the HIT and HITT groups, but a significant reduction was seen in death caused by thrombosis in both groups (P=0.005 and P<0.001
respectively). Argatroban was associated with more rapid resolution of thrombocytopenia and no increase in bleeding. Argatroban has also been shown to be more effective than heparin for coronary reperfusion after the use of recombinant tissue plasminogen activator (rt-PA) in acute myocardial infarction.36

The use of warfarin with argatroban results in prolongation of the INR beyond that produced by warfarin alone. For doses up to 2 μg kg⁻¹ min⁻¹, the equivalent INR on warfarin alone (INRW) can be calculated from the INR for cotherapy of warfarin and argatroban (INRWₐ) according to a published graph.48 The error associated with this prediction is ±0.4 units. For argatroban doses >2 μg kg⁻¹ min⁻¹, the relationship is less predictable and the error of prediction is ±1 units. The equivalent INR on warfarin alone (INRW) cannot be predicted reliably from the INRWₐ at doses greater than 2 μg kg⁻¹ min⁻¹.48

Other alternatives in HIT
There are no convincing data available for the use of the following alternatives. However, they may have a role as an adjunct with other anticoagulants.23 67
(i) intravenous immunoglobulins (IgG class);
(ii) platelet transfusion—can increase new thromboembolic complications and is not indicated currently even as an adjunct in the treatment of HIT;
(iii) plasma exchange—its effectiveness is in doubt;
(iv) fresh frozen plasma—some use in HIT complicated by warfarin therapy;
(v) glycoprotein IIb/IIIa inhibitor.

Post-heparin thrombosis
Studies have shown that HIT antibodies are capable of activating platelets in a non-heparin-dependent manner, as a result of the generation of ‘superactive’ HIT antibody.1 Using serum of patients with HIT/HITT, peripheral blood monocytes and monoclonal antibodies specific for H-PF4, researchers have shown that monoclonal antibodies and antibodies from patients with HIT/HITT induce monocyte activation with secretion of interleukin 8 and cell-surface procoagulant activity. The time-dependence of these changes in vitro (>6 h) far exceeds the short incubation period (<1 h) required for platelet activation by H-PF4 antibodies. Hence, it is suggested that these changes in the monocyte could amount to the pathogenesis of thrombi after the discontinuation of heparin.5

Summary
It is important to have a high index of clinical suspicion in a patient with a falling platelet count who is receiving heparin. It is imperative to discontinue all sources of heparin even before the laboratory confirmation of HIT. Platelet transfusion is contraindicated as this can exacerbate the serious thrombotic complications. Circulating antibodies bind to the transfused platelets and release platelet microparticles, leading to a thrombotic state. Treatment is intended to reduce the thromboembolic complications. There are several pharmaceutical agents available for the treatment of HIT. Before starting any of these agents, the clinician should decide which of them is safe and effective for the individual patient. Lepirudin is an irreversible, direct thrombin inhibitor that has shown effectiveness in treating patients with HIT type II. It does not cross-react with heparin and can be readily monitored with the aPTT and ECT. Disadvantages include a prolonged half-life, prolongation of the prothrombin time, possible antibody formation, and the requirement for dose adjustments in patients with renal impairment. Argatroban is the newest agent used for HIT type II. It binds reversibly to thrombin and is monitored with the aPTT. Patients who require anticoagulation and have renal impairment may benefit from the use of argatroban because of its hepatic metabolism. A disadvantage of this agent is prolongation of the prothrombin time (necessitating additional monitoring in patients who are also receiving warfarin), and dose adjustment in patients with hepatic impairment. Danaparoid, prostacyclin analogues and desirudin, although previously used in HIT, are not licensed for the treatment of HIT or HITT.

References


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