The management of heparin-induced thrombocytopenia

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Abstract

The Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology has produced a concise practical guideline to highlight the key issues in the management of heparin-induced thrombocytopenia (HIT) for the practicing physician in the UK. The guideline is evidence-based and levels of evidence are included in the body of the article. All patients who are to receive heparin of any sort should have a platelet count on the day of starting treatment. For patients who have been exposed to heparin in the last 100 d, a baseline platelet count and a platelet count 24 h after starting heparin should be obtained. For all patients receiving unfractionated heparin (UFH), alternate day platelet counts should be performed from days 4 to 14. For surgical and medical patients receiving low-molecular-weight heparin (LMWH) platelet counts should be performed every 2–4 d from days 4 to 14. Obstetric patients receiving treatment doses of LMWH should have platelet counts performed every 2–4 d from days 4 to 14. Obstetric patients receiving prophylactic LMWH are at low risk and do not need routine platelet monitoring. If the platelet count falls by 50% or more, or falls below the laboratory normal range and/or the patient develops new thrombosis or skin allergy between days 4 and 14 of heparin administration HIT should be considered and a clinical assessment made. If the pretest probability of HIT is high, heparin should be stopped and an alternative anticoagulant started at full dosage unless there are significant contraindications when laboratory tests are performed. Platelet activation assays using washed platelets have a higher sensitivity than platelet aggregation assays but are technically demanding and their use should be restricted to laboratories experienced in the technique. Non-expert laboratories should use an antigen-based assay of high sensitivity. Only IgG class antibodies need to be measured. Useful information is gained by reporting the actual optical density, inhibition by high concentrations of heparin, and the cut-off value for a positive test rather than simply reporting the test as positive or negative.

In making a diagnosis of HIT the clinician’s estimate of the pretest probability of HIT together with the type of assay used and its quantitative result (enzyme-linked immunosorbent assay, ELISA, only) should be used to determine the overall probability of HIT. Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant. For patients with strongly suspected or confirmed HIT, heparin should be stopped and full-dose anticoagulation with an alternative, such as lepirudin or danaparoid, commenced (in the absence of a significant contraindication). Warfarin should not be used until the platelet count has recovered. When introduced in combination with warfarin, an alternative anticoagulant must be continued until the International Normalised Ratio (INR) is therapeutic for two consecutive days. Platelets should not be given for prophylaxis. Lepirudin, at doses adjusted to achieve an activated partial thromboplastin time (APTT) ratio of 1:5–2:5, reduces the risk of reaching the composite endpoint of limb amputation, death or new thrombosis in patients with HIT and HIT with thrombosis (HITT). The risk of major haemorrhage is directly related to the APTT ratio, lepirudin levels and serum creatinine levels. The patient’s renal function needs to be taken into careful consideration before treatment with lepirudin is commenced. Severe anaphylaxis occurs rarely in recipients of lepirudin and is more common in previously exposed patients. Danaparoid in a high-dose regimen is equivalent to lepirudin in the treatment of HIT and HITT. Danaparoid at prophylactic doses is not recommended for the treatment of HIT or HITT. Patients with previous HIT who are antibody negative (usually so after >100 d) who require cardiac surgery should receive intraoperative UFH in preference to other anticoagulants that are less validated for this purpose. Pre- and postoperative anticoagulation should be with an anticoagulant other than UFH or LMWH. Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody negative if possible. They should then proceed as above. If deemed appropriate early surgery should be carried out with an alternative anticoagulant. We recommend discussion of these complex cases requiring surgery with an experienced centre. The diagnosis must be clearly recorded in the patient’s medical record.

Keywords: heparin-induced thrombocytopenia, guideline.
Objectives

Recently there have been a number of good reviews of HIT (if associated with thrombosis often referred to as HITT, if not as isolated HIT) and its treatment (Chong, 2003; Warkentin, 2003; Hirsh et al, 2004; Warkentin & Greinacher, 2004a). The objective of this guideline is not, therefore, to provide an extensive review but to highlight the key issues and to produce practical guidance for the practicing physician managing HIT in the UK.

Methods

The guideline was drafted by a working party of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The term ‘heparin-induced thrombocytopenia’ was combined with the terms ‘pathology’, ‘laboratory tests’, ‘diagnosis’, ‘clinical presentation’, ‘natural history’ and ‘treatment’ in a search of PubMed and Embase to identify key references along with a search using ‘heparin-induced thrombocytopenia’ as the only term but restricted to the title of the article. The search was extended to December 2005 but limited to English language papers. The references in recent reviews (Chong, 2003; Warkentin, 2003; Hirsh et al, 2004; Warkentin & Greinacher, 2004a) were also examined to ensure key references were not missed. Two of the authors examined the retrieved papers, agreed on the studies to include, and assigned levels of evidence. If not initially in agreement they came to a consensus. Recommendations are graded according to the level of evidence according to the Agency for Healthcare Research and Quality (AHRQ) formerly the Agency for Health Care Policy and Research (AHCPR) at http://www.ahrq.gov (Appendix 1).

Pathology

The pathophysiology of HIT is covered in many reviews (Warkentin, 2003; Kelton, 2005). HIT is caused by the development of an IgG antibody that recognises multi-molecular complexes of platelet factor 4 (PF4) and heparin (Rauova et al, 2005). PF4 is a 70-amino acid protein that self-associates to form tetramers of approximately 31 kDa. A ring of positively charged amino acids around the tetramer allows interaction with glycosaminoglycans. The antibodies in HIT recognise a heparin-induced conformational change in the PF4 tetramer (Horsewood et al, 1996). The ability to induce the conformational change depends on the chain length and degree of sulphation of the glycosaminoglycan, which explains the differences in incidence of HIT observed with different heparins. PF4/heparin complexes bind to platelet surfaces. The HIT antibodies recognise the neoantigens on the PF4 tetramers. This leads to HIT-IgG/PF4/heparin complexes forming on the platelet surface. It is thought that IgG Fc regions bind and cross-link the platelet FcError.

Clinical presentations and diagnosis

The frequency of HIT in different settings has been comprehensively reviewed (Lee & Warkentin, 2004). It is important to distinguish the frequency of antibody detection, antibody formation with thrombocytopenia (HIT), and HITT. The incidence of HIT is greater with bovine than with porcine heparin and has generally been found to be greater with UFH than with LMWH (Martel et al, 2005). All heparins used in the UK are of porcine origin. The frequency of HIT is greater in surgical than in medical patients. In orthopaedic patients given subcutaneous prophylactic heparin, the incidence is approximately 5% with UFH and 0.5% with LMWH (Warkentin et al, 2000; Lee & Warkentin, 2004). In medical patients given therapeutic porcine UFH it is approximately 0.7% (Lee & Warkentin, 2004) and subcutaneous UFH in medical patients gave a rate of 0.8% (Girolami et al, 2003). The incidence in medical patients given LMWH for prophylaxis or treatment was found to be 0.8% (Prandoni et al, 2005). This is surprising given that LMWH has generally been found to carry a 10-fold lower risk than UFH in a meta-analysis (Martel et al, 2005), and while this analysis contained mostly orthopaedic studies, other studies in medical patients have shown a similar pattern (Lindhoff-Last et al, 2002; Pohl et al, 2005; Prandoni et al, 2005). The risk is very low in obstetric patients given LMWH, for example, only one possible case was observed in 1167 pregnant women given LMWH in three studies (Sanson et al, 1999; Ellison et al, 2000; Lepercq et al, 2001), although only 6% received full treatment doses; the rest received prophylaxis. It has been suggested that medical and obstetric patients receiving prophylactic or therapeutic LMWH do not need routine platelet monitoring (Lee & Warkentin, 2004; Warkentin & Greinacher, 2004a), but this recommendation pre-dated the paper by Prandoni et al (2005). We agree with this recommendation for obstetric patients receiving prophylaxis, although HIT should be considered if they develop skin reactions or thrombosis. Skin lesions occur at the site(s) of subcutaneous injection and range in appearance from indurated erythematous nodules or plaques to frank skin necrosis.

If HIT develops the platelet count typically begins to fall 5–10 d after starting heparin although in patients who have received heparin in the previous 3 months it can have a rapid onset because of pre-existing antibodies. Occasionally, the onset can occur after more than 10 d of heparin exposure but it is rare after 15 d. The platelet count normally falls by >50% and has a median nadir of 55 × 10⁹ per l (Warkentin & Kelton, 2001; Warkentin, 2003). Severe thrombocytopenia (platelets <15 × 10⁹ per l) is unusual. Patients (10–20%) who develop HIT whilst receiving subcutaneous injections develop skin lesions at the injection site (Warkentin, 1996). Half of the patients who develop HIT will have associated thrombosis. Furthermore, in those presenting without thrombosis (isolated HIT) there is a high risk of subsequent thrombosis if heparin is not stopped and an alternative anticoagulant given in therapeutic doses.
If HIT is suspected on the basis of a fall in the platelet count in a patient receiving heparin, the probability of HIT should initially be judged on clinical grounds. Four features are particularly helpful in estimating the likelihood of HIT (Warkentin, 2003): the degree of thrombocytopenia, the timing of the onset, the presence of new or progressive thrombosis and whether an alternative cause of thrombocytopenia is likely. A scoring system has been devised to assess the pretest probability (Table I) (Warkentin & Heddle, 2003; Warkentin, 2003). If the pretest probability is high, heparin should be stopped and an alternative anticoagulant given whilst laboratory tests are performed.

**Recommendations**

- All patients who are to receive heparin of any sort should have a platelet count performed on the day of starting treatment. Grade C Level IV.
- For patients who have been exposed to heparin in the last 100 d a baseline platelet count and a platelet count 24 h after starting heparin should be obtained. Grade C Level IV.
- For all patients receiving UFH, alternate day platelet counts should be performed from days 4 to 14. Grade C Level IV.
- For surgical and medical patients receiving LMWH, platelet counts should be performed every 2–4 d from days 4 to 14. Grade C Level IV.
- Obstetric patients receiving treatment doses of LMWH should have platelet counts performed every 2–4 d from days 4 to 14. Obstetric patients receiving prophylactic LMWH are at low risk and do not need routine platelet monitoring. Grade C Level IV.
- If the platelet count falls by 50% or more and/or the patient develops new thrombosis or skin allergy between days 4 and 14 of heparin administration, HIT should be considered and a clinical assessment made. Grade C Level IV.
- If the pretest probability of HIT is high, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed unless there are significant contraindications. Grade C Level IV.

**Laboratory tests**

Tests for HIT antibodies can be classified as platelet activation assays or immunological assays using PF4 as the antigen.

### Platelet activation assays

A standard platelet aggregometer can be used to detect aggregation of normal platelets in the presence of patient plasma and heparin (Chong et al, 1993; Warkentin & Greinacher, 2004b). At best, the sensitivity of this method is 85% (Warkentin & Greinacher, 2004b). Donor selection is important, as platelet responsiveness to HIT antibodies varies. HIT antibodies produce activation of platelets at 0–10 IU/ml heparin that is no longer seen at 100 U/ml heparin. Greater sensitivity can be achieved using washed platelet methods. A variety of platelet activation endpoints can then be used, including release of radioactive serotonin (Warkentin et al, 1992). Unfortunately, washed platelet activation assays are technically demanding, and performance varies widely among laboratories (Eichler et al, 1999). The use of washed platelet activation assays should be restricted to laboratories experienced in the technique.

### Antigen assays

There are two commercial ELISAs available to detect surface bound PF4-heparin or the polyvinylsulphate-PF4 (Asserachrom

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**Table I. Estimating the pretest probability of HIT: the ‘four Ts’.

| Points (0, 1 or 2 for each of four categories: maximum possible score = 8) |
|----------------|-------------|-------------|
|                | 2           | 1           | 0           |
| Thrombocytopenia| > 50% fall or platelet nadir 20–100 × 10⁹ per l | 30–50% fall or platelet nadir 10–19 × 10⁹ per l | fall <30% or platelet nadir <10 × 10⁹ per l |
| Timing* of platelet count fall or other sequelae | Clear onset between days 5 and 10; or less than 1 d (if heparin exposure within past 100 d) | Consistent with immunisation but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10 | Platelet count fall too early (without recent heparin exposure) |
| Thrombosis or other sequelae (e.g. skin lesions) | New thrombosis; skin necrosis; post heparin bolus acute systemic reaction | Progressive or recurrent thrombosis; erythematosus skin lesions; suspected thrombosis not yet proven | None |
| Other causes for thrombocytopenia not evident | No other cause for platelet count fall is evident | Possible other cause is evident | Definite other cause is present |


*First day of immunising heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 d more until an arbitrary threshold that defines thrombocytopenia is passed.
IgM type antibodies besides IgG. Warkentin antibodies. HIT than an assay that also detects IgA and IgM class an EIA that detects anti-PF4/polyanion antibodies of only the patients in whom clinical HIT developed. They concluded that HIT immune responses did not differ from that exhibited by and magnitude of IgA and IgM antibody formation in non-detecting non-pathogenic antibodies. Moreover, the frequency antibodies by the GTI EIA worsened test specificity by They found that additional detection of IgA and IgM classes improves or worsens assay operating characteristics. They investigated whether the additional detection of these antibody classes improves or worsens assay operating characteristics. They found that additional detection of IgA and IgM antibodies by the GTI EIA worsened test specificity by detecting non-pathogenic antibodies. Moreover, the frequency and magnitude of IgA and IgM antibody formation in non-HIT immune responses did not differ from that exhibited by patients in whom clinical HIT developed. They concluded that an EIA that detects anti-PF4/polyanion antibodies of only the IgG class has greater diagnostic usefulness in revealing clinical HIT than an assay that also detects IgA and IgM class antibodies.

Diagnostic interpretation
In clinically suspected HIT, washed platelet activation assays and antigen assays have similar high sensitivity and a negative test makes HIT unlikely. Sensitivity is significantly less using standard platelet aggregometry (Greinacher et al, 1994). Diagnostic specificity is greater with the washed platelet activation assays compared with antigen assays, as the latter are more likely to detect clinically insignificant antibodies (Warkentin et al, 2000). The clinician’s estimate of the pretest probability of HIT should be taken into account, together with the type of assay used and its quantitative result, to determine the post-test probability of HIT (Warkentin et al, 2003). We suggest laboratories report the actual optical density, inhibition by heparin and the cut-off for a positive test rather than simply reporting the test as positive or negative. The sensitivities, specificities, and so, likelihood ratios for tests depends on the cut-offs chosen. It has been estimated that a positive serotonin release assay (90% release) and a strongly positive ELISA (optical density >1.5) have likelihood ratios of 20 and 10, respectively, for HIT postcardiac surgery (Warkentin & Greinacher, 2004b).

Recommendations

- Platelet activation assays using washed platelets have a higher sensitivity than platelet aggregation assays but are technically demanding and their use should be restricted to laboratories experienced in the technique. Grade C Level IV.
- Non-expert laboratories should use an antigen assay of high sensitivity. Only the IgG class needs to be measured. Useful information is gained by reporting the actual optical density, inhibition by heparin, and the cut-off for a positive test rather than simply reporting the test as positive or negative. Grade B Level III.
- In making a diagnosis of HIT the clinician’s estimate of the pretest probability of HIT together with the type of assay used and its quantitative result (ELISA only) should be used to determine the post-test probability of HIT. Grade C Level IV.

Treatment

General principles
In the UK the alternative anticoagulants available for use in HIT are danaparoid and lepirudin. Argatroban is used in North America. LMWH is not an appropriate alternative if HIT develops during treatment with UFH as there is cross-reactivity in vivo in approximately 50% of cases (Keeling et al, 1994; Ramakrishna et al, 1995; Slocum et al, 1996; Vun et al, 1996). Fondaparinux, a synthetic anticoagulant modelled after the antithrombin-binding pentasaccharide, may bind to PF4 but its length is shorter than the 10–12 saccharides reported to be required for binding to PF4 to result in strong reactivity with HIT antibodies. Thus, fondaparinux is expected to be non-immunogenic and unable to cause HIT. Warkentin et al (2005b) tested 2726 patients randomised to receive antithrombotic prophylaxis with fondaparinux or enoxaparin following hip or knee surgery. They found that anti-PF4/heparin antibodies were generated at similar frequencies in patients treated with fondaparinux or enoxaparin. Although antibodies reacted equally well in vitro against PF4/UFH and PF4/ enoxaparin, and sometimes weakly against PF4/danaparoid, none reacted against PF4/fondaparinux, including even those
sera obtained from patients who had formed antibodies during fondaparinux treatment. At high concentrations, however, fondaparinux inhibited binding of HIT antibodies to PF4/polysaccharide, indicating that PF4/fondaparinux interactions occur. No patient developed HIT. They concluded that, despite similar immunogenicity of fondaparinux and LMWH, PF4/fondaparinux (but not PF4/LMWH) is recognised poorly by the antibodies generated, suggesting that the risk of HIT with fondaparinux is likely to be very low. Warfarin can increase the risk of microvascular thrombosis in HIT and its introduction should be delayed until there has been substantial resolution of the thrombocytopenia. It should then be introduced with overlap of the alternative anticoagulant (Warkentin et al, 1997; Smythe et al, 2002).

Bleeding is uncommon in HIT and as platelet transfusions could theoretically contribute to thrombotic risk they are relatively contraindicated (Greinacher & Warkentin, 2004).

Whichever alternative anticoagulant is used, it is important to give it in appropriate doses as discussed below as there is evidence for treatment failure in cases where doses deemed appropriate for prophylaxis in other circumstances have been used in HIT. This pertains to all cases whether or not they are complicated by thrombosis at the time of diagnosis. The evidence for this is the high failure rate with a prophylactic dose of danaparoid (750 u.b.d. or t.i.d.) in comparison with dose-adjusted lepirudin, or higher (‘therapeutic’) doses of danaparoid (2500 U bolus followed by continuous infusion) in the Heparin Associated Thrombocytopenia (HAT) studies (Farner et al, 2001). It has been suggested that for patients with HIT routine ultrasonography of the lower limb veins is performed to look for asymptomatic DVT (Warkentin & Greinacher, 2004a); we do not believe this is necessary as all patients will receive full-dose anticoagulation and there is no evidence for prolonged anticoagulation in asymptomatic venous thromboembolism.

Major bleeding commonly complicates the treatment of HIT with an alternative anticoagulant (Greinacher et al, 2000). Clinical decision making should address the likely risks and benefits of the available treatment strategies. A therapeutic dosing regimen is given in Table II.

**Table II.** Therapeutic dosing regimens for danaparoid and lepirudin in the treatment of acute HIT/HITT.

<table>
<thead>
<tr>
<th></th>
<th>IV Bolus</th>
<th>IV infusion</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid</td>
<td>60–75 kg–2250 U</td>
<td>400 U/h for 4 h, 300 U/h</td>
<td>Anti-Xa 0.5–0.8 U/ml</td>
</tr>
<tr>
<td></td>
<td>75–90 kg–3000 U</td>
<td>for 4 h, then 150–200 U/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;90 kg–3750 U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepirudina*</td>
<td>Isolated HIT</td>
<td>None</td>
<td>APTT 1.5–2.5†</td>
</tr>
<tr>
<td></td>
<td>HITT</td>
<td>400 µg/kg</td>
<td>Start at 150 µg/kg/h</td>
</tr>
</tbody>
</table>

*For lepirudin a maximum body weight of 100 kg should be used for dose calculations and dose adjustment is required in renal insufficiency.
†Should correspond to a lepirudin plasma concentration of 0.6–1.4 mg/l.

### Recommendations

- **Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant.** Grade C level IV.
- **For patients with strongly suspected or confirmed HIT, heparin should be stopped and full-dose anticoagulation with an alternative, such as lepirudin or danaparoid, commenced (in the absence of a significant contraindication).** Grade B level III.
- **Warfarin should not be used until the platelet count has recovered.** When introduced, an alternative anticoagulant must be continued until the INR is therapeutic for two consecutive days. Grade C level IV.
- **Platelets should not be given for prophylaxis.** Grade C level IV.

#### Lepirudin

Lepirudin is a 65-amino acid peptide with a molecular weight of approximately 7000 Da produced by recombinant technology. It is a direct, irreversible thrombin inhibitor, binding both free and clot-bound thrombin. It has a half-life of 60–90 min with renal excretion. The use of lepirudin in the treatment of HIT has been extensively reviewed (Greinacher, 2004; Hirsh et al, 2004; Warkentin, 2004). A systematic review of the literature identified three key prospective trials (Greinacher et al, 1999a,b; Eichler et al, 2002) that contain data on large numbers of patients with isolated HIT or HITT who have been treated with lepirudin. In these studies, HAT 1–3, the comparative group were historical controls or patients from the participating centres who fulfilled the same inclusion criteria but were not enrolled in the prospective study of lepirudin for a variety of reasons. The combined results of these studies have been published as two meta-analyses, the first on treatment of patients with HITT (Greinacher et al, 2000), the second on patients with HIT not complicated at diagnosis by a thrombotic event (Lubenow et al, 2004). Both meta-analyses assessed the composite endpoint of death, new thromboses or limb amputation and in addition gave data on bleeding events.
One hundred and thirteen patients with HITT received a bolus of lepirudin followed by a continuous infusion to maintain an APTT ratio of 1.5–2.5 (0.4 mg/kg then 0.15 mg/kg h (n = 105) or 0.2 mg/kg then 0.1 mg/kg h (n = 8)). Compared with 75 historical controls that received danaparoid (n = 24), coumarins (n = 21) or other treatments (n = 30), those treated with lepirudin had a lower incidence of reaching the composite endpoint, which was statistically significant. When the individual endpoints were analysed there were trends towards reduced mortality and limb amputation, but a significant decrease only in new thrombosis in the lepirudin-treated group (8.9% vs. 17.6%, 6.5% vs. 10.4% and 10.1% vs. 27.2% respectively) (Greinacher et al, 2000).

Ninety-one patients from the three studies who had not sustained a thrombotic episode at the time of diagnosis of HIT and had been treated with dose-adjusted lepirudin (0.1 mg/kg/h) to maintain an APTT ratio of 1.5–2.5 times baseline were compared with 47 controls, who were patients with the same inclusion criteria and were treated at the discretion of the supervising physician but did not receive lepirudin or danaparoid. In the lepirudin-treated group (13 (14.3%) died, four (4.4%) had a new thrombosis and three (3.3%) had a limb amputation, [18 (19.8%) had one or more of these endpoints]. In comparison, in the control group the figures were [10 (21.3%) deaths, seven (14.9%) new thromboses and zero (0%) limb amputations, with a combined endpoint reached in 14 (29.8%). The reduction in new thromboses and the combined endpoint was statistically significant.

As in all scenarios where antithrombotic drugs are used, the benefit is partial offset by haemorrhagic complications. In the meta-analysis of treatment of HIT with a bolus and infusion regimen the incidence of both bleeding and major bleeding (defined as requiring transfusion) was significantly higher in the lepirudin-treated group (42% vs. 23.6%; P = 0.001 and 18.8% vs. 7.1%; P = 0.02). Therefore, the reduction in the new thrombosis rate from 27.2% to 10.6% in this study was offset by an increase in major haemorrhage from 7.1% to 18.8%. In the meta-analysis of treatment of HIT by continuous infusion without a bolus injection, major bleeding was seen in 14.3% and 8.5% of patients and controls respectively.

Both studies addressed the associated relationship between the APTT ratio and haemorrhagic complications. In both, higher APTT ratios were associated with an increased risk of major haemorrhage. High APTT ratios in turn correlated directly with lepirudin and creatinine levels indicating that additional consideration is required when prescribing lepirudin for patients who have or are likely to develop renal impairment.

Although an APTT ratio of 1.5–2.5 has been recommended (Greinacher et al, 2000) it should be checked that this corresponds to a lepirudin concentration of approximately 0.6–1.4 mg/l with the APTT reagent in use. An alternative to the APTT is the ecarin clotting time (ECT) (Nowak & Bucha, 1996) which is more linear at higher lepirudin concentrations.

Lepirudin is a foreign protein that frequently induces antibodies that can prolong its effect (Eichler et al, 2000). This might require a significant reduction in the lepirudin dosage. It is speculated that this is because lepirudin is excreted renally and lepirudin/antibody complexes are too large for renal excretion, resulting in prolongation of the half-life of the drug (Eichler et al, 2000). Twenty-six possible cases of anaphylaxis/severe allergy to lepirudin have been described in databases from 1994 to 2002 (Greinacher et al, 2003). Nine patients were judged to have had severe anaphylaxis within minutes of intravenous lepirudin and four were fatal. In these four cases, a previous uneventful treatment course with lepirudin was identified (1–12 weeks earlier). Approximately 35,000 patients have received lepirudin and the authors estimated the risk of anaphylaxis as approximately 0.015% on first exposure and 0.16% on re-exposure. A therapeutic dosing regimen is given in Table II.

Recommendations

- Lepirudin at doses adjusted to achieve an APTT ratio of 1.5–2.5 reduces the risk of reaching the composite endpoint of limb amputation, death or new thrombosis in patients with HIT and HITT. Grade B level III.
- The risk of major haemorrhage is directly related to the APTT ratio, lepirudin levels and serum creatinine levels. The patient’s renal function needs to be taken into careful consideration before treatment with lepirudin is commenced. Grade B level III.
- Severe anaphylaxis occurs rarely in recipients of lepirudin and is more common in previously exposed patients. Grade C level IV.

Danaparoid

Danaparoid is a heparinoid composed of heparan sulphate, dermatan sulphate and chondroitin sulphate. Its mechanism of action is not entirely clear but it inhibits factor Xa and, to a much lesser degree, thrombin. Although in about 20% of cases cross-reactivity to the antibodies which mediate HIT, in vitro cross-reactivity to the antibodies which cross-reactivity is rare although well described (Keng & Chong, 2001). Danaparoid has a long half-life and near 100% bioavailability. Anti-Xa assays have been used to monitor its use although it is not clear whether they provide any clinically useful information in most cases. Expert opinion suggests that monitoring may be of value only in patients with severe renal impairment and extremes of body weight (<55 and >90 kg) (Farner et al, 2001). Danaparoid is approved in the European Union for use in two distinct dosing regimens. Published data report on the use of a low-dose (‘prophylactic’) regimen of 750 anti-Xa units b.d. or t.i.d. subcutaneously and a higher dose (‘therapeutic’) regimen, which consists of a bolus injection followed by a reducing dose continuous infusion (2500 anti-Xa units i.v. followed by 400 U/h for 4 h, then 300 U/h for 4 h, then 200 U/h as a
The treatment of HIT is complex, requiring careful consideration of the clinical context, the risk of thrombosis, and the potential for bleeding. In patients with HIT, the choice of anticoagulant should be based on a balance of potential benefits and risks. Danaparoid is a heparinoidal anticoagulant that has been extensively studied in the treatment of HIT. It is effective in preventing new thrombotic events and has a favorable safety profile.

There is a growing body of evidence supporting the use of danaparoid in the treatment of HIT. A meta-analysis of studies comparing danaparoid with lepirudin found that danaparoid was associated with a lower rate of new thrombotic events than treatment with higher doses of lepirudin or danaparoid (Farner et al., 2001). In this study, a prospectively recruited cohort of patients with HIT who were treated with lepirudin were compared with contemporaneous patients with HIT from the same centres who, for some reason, were not included in the lepirudin treatment group. Patients with HIT were given a full-dose regimen while those with HIT without thrombosis were given lower doses. The high-dose regimens were lepirudin 0.4 mg/kg i.v. bolus followed by 0.15 mg/kg/h i.v. continuous infusion to maintain an APTT ratio of 1.5–2.0 compared with the patients baseline, or 0.2 mg/kg bolus followed by 0.1 mg/kg/h dose, adjusted if the patient had received thrombolysis. The danaparoid full-dose regimen consisted of 2500 anti-Xa units i.v. bolus followed by a continuous infusion of 400 U/h for 4 h followed by 300 U/h for 4 h followed by 200 U/h. The low-dose treatments were lepirudin 0.1 mg/kg/h, dose-adjusted to an APTT ratio of 1.5–2.0 with no bolus or danaparoid 750 anti-Xa units b.d. or t.i.d. Efficacy data were available on 294 patients (danaparoid 126). At 42 d follow-up there were no differences between treatments for the composite endpoint of death, amputation or new thrombosis. There was a nonsignificant increase in new thrombotic events in patients given danaparoid at low doses compared with full-dose danaparoid or dose-adjusted lepirudin. Patients without thrombosis at presentation who were treated with danaparoid were significantly more likely to reach the combined endpoint than those treated with lepirudin (P = 0.02). The most likely explanation of these findings is that, for patients with HIT without thrombosis, low-dose danaparoid is insufficient treatment. On the other hand, full-dose danaparoid was equivalent to lepirudin at preventing new thrombosis. Major bleeding was more common in the patients who received lepirudin but this probably reflects the low level of anticoagulation in the significant number of patients who received only prophylactic doses of danaparoid.

In a randomised study of 42 patients, the effectiveness of danaparoid was adjudged significantly superior to dextran (Chong et al., 2001).

### Recommendations

- Danaparoid at prophylactic doses is not recommended for the treatment of HIT or HITT. Grade B Level III.

### Anticoagulation in patients with a history of HIT

Following the development of hypersensitivity to a drug, it is generally accepted that further exposure should be avoided if possible. It would seem reasonable in the vast majority of cases where a patient with previous HIT requires a period of anticoagulation or anticoagulant prophylaxis to recommend use of an alternative to UFH or LMWH.

### Haemodialysis

Danaparoid and lepirudin have both been used (Fischer, 2004). Regimens for alternate day dialysis are given in Table III.

### Cardiac surgery

In cardiac surgery the depth of experience with UFH, the established near-patient monitoring, and the rapid reversal indicate that its use should be considered. There is, therefore, a rationale and some data that support the safe use of UFH in patients with previous HIT. Firstly, in patients who develop typical HIT there is no relationship between the day of onset and previous heparin exposure. Further, in patients with rapid onset HIT there is an association with recent heparin exposure (previous 100 d) but not with more remote heparin exposure. Finally, HIT antibodies are transient with a median time to disappearance of 50–80 d. These data suggest that the antibodies that mediate HIT are transient, that there is no anamnestic immune response in HIT and that acute onset HIT represents recurrence because of renewed heparin exposure.

There are reports of successful heparin re-exposure to permit cardiac and vascular surgery in patients with previous HIT (Potzsch et al., 2000; Warkentin & Kelton, 2001; Nuttall et al., 2003). Regimens for alternate day haemodialysis in patients who have previously had HIT (Fischer, 2004).

<table>
<thead>
<tr>
<th>IV Bolus</th>
<th>Monitoring</th>
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<tbody>
<tr>
<td>Danaparoid</td>
<td>3750 (2500) U* before first and second dialyses; 3000 U before third dialysis; then according to predialysis anti-Xa level</td>
</tr>
<tr>
<td>*&lt;0.3</td>
<td>80–150 µg/kg before dialysis</td>
</tr>
<tr>
<td>0.3–0.35</td>
<td>0 U</td>
</tr>
<tr>
<td>0.35–0.4</td>
<td>2000 (1500) U</td>
</tr>
<tr>
<td>&gt;0.4</td>
<td>0 U</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>0.5–1.0 mg/kg before dialysis</td>
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<tr>
<td></td>
<td>APTT 2.0–2.5</td>
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</table>

*For danaparoid use doses in parentheses for patients <55 kg.
et al, 2003). In patients with recent or current HIT who require cardiac surgery, the risk associated with further heparin exposure is probably much greater, and therefore, it should be avoided if possible. Several strategies, some including the use of UFH offset by the use of an anti-platelet agent, such as tirofiban or epoprostenol, have been reported (Koster et al, 2000a,b, 2001; Aouifi et al, 2001; Mertzlufft et al, 2000). The number of patients included in these reports is small and the experience confined to very few centres. In addition, the intraoperative complications of the prostacyclin analogues can be severe and difficult to manage, while the manufacturer of tirofiban does not recommend its use for this indication. There are published protocols for the use of lepirudin, bivalirudin and danaparoid in cardiac surgery (Warkentin & Greinacher, 2003; Poetzsch & Madlener, 2004; Warkentin & Koster, 2005). Monitoring by ECT for lepirudin and bivalirudin and anti-Xa assay for danaparoid is recommended. If the postoperative period is complicated by renal failure, problems with the prolonged half-life of the drugs and the absence of an antidote may emerge. The largest series of lepirudin use in this context reported thrombosis-free survival in 54 of 57 (95%) patients (Koster et al, 2000b). Excessive blood loss and slow drug elimination was seen in the four patients with pre-existing renal failure but there were no haemorrhagic deaths. In 53 patients who managed using a fixed dose danaparoid regimen, severe postoperative bleeding occurred in 21% of patients. In addition, clots were seen in the operative field in a third of patients (Magnani et al, 1997).

Recommendations

• Patients with previous HIT who are antibody negative (usually so after >100 d) who require cardiac surgery should receive intra-operative UFH in preference to other anticoagulants that are less validated for this purpose. Pre- and postoperative anticoagulation should be with an anticoagulant other than UFH or LMWH. Grade C level IV.

• Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody negative if possible. They should then proceed as above. If deemed appropriate, early surgery should be carried out with an alternative anticoagulant. Grade C level IV.

• We recommend discussion of these complex cases requiring surgery with an experienced centre. Grade C level IV.

Patient information and record keeping

The diagnosis of HIT should be clearly recorded in the patient’s notes and marked as a serious allergy. The condition should be clearly explained to the patient and an information leaflet may be helpful in this respect. The patient should be issued with an antibody card.

Recommendation

• The diagnosis must be clearly recorded in the patient’s medical record. Grade C, level IV.

Conflicts of interest

DK and HW had no conflicts of interest to declare. SD has received an honorarium via Organon for some consultancy work.

Disclaimer

Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

The Haemostasis and Thrombosis Taskforce meet every 6 months and will review these guidelines if any major developments occur or by November 2009 at the latest.

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## Appendix 1

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials.</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence obtained from at least one other well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

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<tr>
<th>Grade</th>
<th>Recommendation (based on AHCPR)</th>
</tr>
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<tbody>
<tr>
<td>A (evidence levels Ia, Ib)</td>
<td>Requires at least one randomised controlled trial as part of the body of the literature of overall good quality and consistency addressing the specific recommendation</td>
</tr>
<tr>
<td>B (evidence levels IIa, IIb, III)</td>
<td>Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation</td>
</tr>
<tr>
<td>C (evidence level IV)</td>
<td>Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality</td>
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