Monitoring and management of heparin-induced thrombocytopenia

Low molecular weight heparins have been used to reduce thromboembolic risk for at least 20 years, but their use is not without risk. This article considers the incidence, monitoring, treatment and lack of insight about heparin-induced thrombocytopenia – a potentially fatal complication of low molecular weight heparin use.

Low molecular weight heparins have been commonly used for over two decades by many medical and surgical specialties. They are at least as effective as other means of thrombosis prevention and are widely used in orthopaedic patients, particularly those undergoing lower limb joint arthroplasty (Leyvraz et al, 1991; Mohr et al, 1993; Wolf, 1994).

Their main advantage is that they can be used without laboratory monitoring and they have less bleeding compared with unfractionated heparin for a given antithrombotic effect (therapeutic index) (Wolf, 1994). Several types of low molecular weight heparin are commonly used including enoxaparin (Clexane, Sanofi-Aventis, Guildford), dalteparin (Fragmin, Pharmacia, Milton Keynes) and tinzaparin (Innohep, Leo Pharmaceuticals, Princes Risborough), with bleeding and thrombocytopenia the most common complications (Joint Formulary Committee, 2006).

Bleeding may occur at various locations: the operative site, epidural space, intrahepatic or retroperitoneal bleeding (Houde and Steinberg, 1999; Shaieb et al, 1999; Stern et al, 2000; Antonelli et al, 2000). Intracerebral haemorrhage following the use of low molecular weight heparin has occurred following neurosurgical and orthopaedic procedures with tragic consequences (Dickinson et al, 1998; Lilikakis et al, 2006).

Heparin-induced thrombocytopenia

Clinical

Heparin-induced thrombocytopenia is one of the most important immunohaematological problems in clinical medicine. It can be associated with thrombosis which is independent of heparin type, dose or route of administration (King and Kelton, 1984; Chong, 1995).

Low molecular weight heparin is associated with two forms of thrombocytopenia. Type I (non-immune mediated) causes a mild thrombocytopenia, typically occurring 1–4 days after starting low molecular weight heparin, with screening tests for heparin-induced thrombocytopenia antibodies negative. No data suggest that type I heparin-induced thrombocytopenia has an increased risk of thrombosis and it is attributable to a direct, reversible, proaggregatory effect of platelets (Antonelli et al, 2000).

Type II heparin-induced thrombocytopenia (immune mediated) typically appears 5 or more days after the start of heparin therapy, but develops more rapidly in patients previously exposed to heparin (Shaieb et al, 1999). It is clinically more important as it can cause life-threatening thromboses. Onset is independent of heparin type, dosage or route of administration and the diagnosis needs both the presence of heparin antibodies and a reduction in platelet count of 50%. Cessation of heparin triggers a rise in the platelet count, usually within 5–7 days, and a delay in the normalization of the platelet count should lead to investigation of other causes of thrombocytopenia.

The estimated incidence of type II heparin-induced thrombocytopenia is between 1% with low molecular weight heparin and 5% with unfractionated heparin. There are variations depending on heparin type (bovine heparins are associated with a higher risk than porcine, so nearly all heparins used in UK are porcine in origin), type of patient (surgical patients are at higher risk than medical patients) and route of administration (intravenous gives a higher risk than subcutaneous).

Thrombosis is the principal risk causing ischaemia and subsequent organ failure to limbs and/or vital organs. It can occur in up to 30% of type II heparin-induced thrombocytopenia – termed the 'white clot syndrome' (Chong, 1995). Arterial thromboses secondary to type II heparin-induced thrombocytopenia commonly lead to cerebrovascular accident and myocardial infarction, with venous thromboses causing deep vein thrombosis and pulmonary embolism, and with disseminated intravascular coagulation as a potential devastating consequence. Previous reports have documented a mortality ranging from 15% to 30% (Shaieb et al, 1999; Antonelli et al, 2000). In a small study carried out in the authors' unit, there was a 8.7% incidence of asymptomatic thrombocytopenia, defined as a platelet count of less than 50% of the preoperative value, in patients receiving low molecular weight heparin following lower limb arthroplasty

Mr BA Rogers *is Specialist Registrar in Trauma and Orthopaedics and*
Mr NJ Little *is Specialist Registrar in Trauma and Orthopaedics and*
Dr C Jones *is Specialist Registrar in Anaesthetics and Intensive Care, St George's Hospital, London SW17 0QT*

Correspondence to: Mr BA Rogers

surgery, highlighting the incidence of patients at risk of heparin-induced thrombocytopenia.

Biology

Heparin-induced thrombocytopenia results from an antibody-mediated response to heparin triggering a reduction in the platelet count (Burgess et al, 1995; Warkentin, 1999). In heparin-induced thrombocytopenia, heparin causes release of platelet factor 4, a 70-amino acid protein, from alpha granules within the platelets. Heparin binds to platelet factor 4 and then undergoes a conformational change, forming an antigenic complex on the surface of platelets (*Figure 1*). Patients develop an antibody (IgG) to the heparin–platelet factor 4 antigenic complex that binds to the heparin–platelet factor 4 immune complex on the platelet surface.

The Fc portion of the antibody then activates the platelets by binding to platelet Fc receptors. The reticuloendothelial system subsequently consumes the activated platelets, platelet microaggregates and IgG-coated platelets causing thrombocytopenia. The activation of platelets together with the generation of procoagulant microparticles and the increase in thrombin generation leads to a pro-thrombotic state responsible for the most serious complications of type II heparin-induced thrombocytopenia.

Guidelines and rationale for monitoring

The clinical importance of heparin-induced thrombocytopenia is driven by four factors:

1. Heparin use is widespread and on the rise
2. Heparin-induced thrombocytopenia is a devastating prothrombotic disease
3. Heparin-induced thrombocytopenia is a severe, immune-mediated drug reaction that can occur in any patient exposed to heparin
4. Heparin-induced thrombocytopenia presents clinicians with a critical medical dilemma.

In response to this the British Society for Haematology produced evidence-based guidelines for the identification and management of heparin-induced thrombocytopenia (Baglin et al, 2006). These guidelines advocate:

1. All patients who receive heparin (of any sort) should have a platelet count on the day of starting treatment
2. All medical and surgical patients receiving low molecular weight heparin or unfractionated heparin should have platelet counts performed every 2–4 days from days 4–14
3. If platelet count falls by over 50% or below normal lab limits and there are features of heparin-induced thrombocytopenia (*Table 1*) one must consider it, so stop heparin and inform a haematologist.

Figure 1. The antibody-mediated response in heparin-induced thrombocytopenia. Adapted from Chong (1995). PF4 = platelet factor 4.

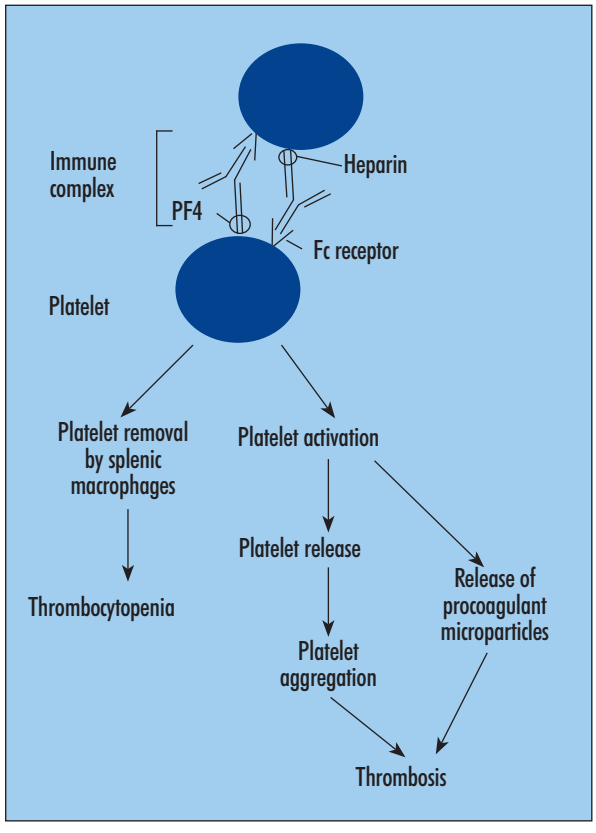

Table 1. Laboratory diagnosis of immune heparin-induced thrombocytopenia

		Category		
Thrombocytopenia	Timing* of platelet count fall or other sequelae	Thrombosis of other sequelae (e.g. skin lesions)	Other causes of thrombocytopenia not evident	**Points (0, 1 or 2 for each category, maximum score = 8)**
>50% fall or platelet nadir 20–100 x 10^9/litre	Clear onset between day 5 and 10, or less than 1 day (if exposed to heparin within past 100 days)	New thrombosis, skin necrosis, post-heparin bolus acute system reaction	No other cause for platelet count is evident	**2**
30–50% fall or platelet nadir 10–19 x 10^9/litre	Consistent with immunization but not clear (i.e. missing platelet counts) or onset of thrombocytopenia after day 10	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis not yet proven	Possible other cause is evident	**1**
Fall < 30% or platelet nadir <10 x 10^9/litre	Platelet count fall too early (without recent heparin exposure)	None	Definite other cause is evident	**0**

From Warkentin and Heddle (2003). Probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low * First day of immunizing heparin exposure is considered day 0

Diagnosis and treatment

The diagnosis of heparin-induced thrombocytopenia requires awareness and a low threshold for suspecting it. If heparin-induced thrombocytopenia is suspected, based upon the above guidelines, a haematologist should be involved early to plan further management. A fall in platelet count alone does not equate to heparin-induced thrombocytopenia and full evaluation of the clinical scenario is needed to predict the probability of heparin-induced thrombocytopenia. Four principal features point to a diagnosis of heparin-induced thrombocytopenia: the degree of platelet fall, the timing of onset, the presence of thrombus and whether an alternative cause of thrombocytopenia is likely (e.g. sepsis or disseminated intravascular coagulation). These factors have been incorporated in a scoring system (Warkentin and Heddle, 2003) to give a probability of heparin-induced thrombocytopenia (*Table 1*).

If a high probability of heparin-induced thrombocytopenia is suspected platelet activation assays or immunological assays with platelet factor 4 as the antigen can be used to make the definitive diagnosis. The aggregation of normal platelets in the patient's plasma with heparin can be detected using a standard platelet aggregometer with a sensitivity of about 85%.

Enzyme-linked immunosorbent assays have a high sensitivity (80–100%) but low specificity for heparin–platelet factor 4, and while some assays detect IgA and IgM, IgG assays have a greater diagnostic sensitivity for heparin-induced thrombocytopenia.

On diagnosing heparin-induced thrombocytopenia the clinician needs to stop heparin and consider the risks and benefits of treatment with an alternative anticoagulant such as lepirudin or danaparoid. Warfarin is not recommended until the platelet count has normalized because in the acute phase it can lead to significant skin necrosis. Platelets should also not be given for prophylaxis as they could contribute to the thrombotic risk.

Lepirudin, a direct, irreversible thrombin inhibitor, reduces the risk of limb amputation, death or new thrombosis if given to achieve an activated partial thromboplastin time ratio of 1.5–2.5. Skin reactions, and hepatic and renal impairment are the commonest side effects of lepirudin use. Danaparoid is a heparinoid, chemically distinct from heparin, inhibiting factor Xa and thrombin, that in a high dose regimen has a similar efficacy to lepirudin (Farner et al, 2001). It is monitored by measuring anti-Xa levels, although some consider monitoring is only necessary in patients with severe renal impairment or extremes of body weight (<55 and >90 kg) (Farner et al, 2001).

Survey and results

In response to a lack of local knowledge regarding this condition, a national survey of 25 district general hospitals, six teaching hospitals and 22 general practice surgeries was conducted regarding the awareness and monitoring of heparin-induced thrombocytopenia (*Table 2*). This survey assessed a cross section of the medical specialties, in both primary and secondary care. The results highlight a near complete lack of awareness of heparin-induced thrombocytopenia monitoring guidelines and indeed none of the units surveyed routinely monitor the platelet count of patients receiving low molecular weight heparin.

Given how commonly low molecular weight heparin is prescribed, the lack of awareness of a complication of its use is of concern and justifies the need for this condition to be highlighted.

Implications and recommendations

Low molecular weight heparins have been used to reduce thromboembolic risk in both primary care and the hospital setting for at least 20 years (Mohr et al, 1993; Wolf, 1994; Imberti et al, 2006). While providing effective pharmacological thromboprophylaxis, their use in orthopaedic surgery is not without risk (Stern et al, 2000; Bickler et al, 2006; Lilikakis et al, 2006).

A significant improvement in platelet count monitoring for patients at risk of heparin-induced thrombocytopenia can be made by the implementation of a simple protocol and an additional full blood count (approximately £1 per test).

All clinicians should be aware of the common side effects and also the rare adverse reactions that may have serious consequences. Following the publication of case reports showing intracranial haemorrhages as a consequence of heparin-induced thrombocytopenia (Lilikakis et al, 2006) and evidence-based guidelines (Baglin et al, 2006), failure to routine monitor for thrombocytopenia in patients receiving low molecular weight heparins may have medicolegal implications.

Table 2. Survey of the awareness of the guidelines for heparin-induced thrombocytopenia and monitoring for patients receiving low molecular weight heparin

	Aware of heparin-induced thrombocytopenia guidelines	Monitor platelet count for patients on low molecular weight heparin
UK district general hospitals	4% (1/25)	0% (0/25)
UK teaching hospitals	17% (1/6)	0% (0/6)
General practitioners	0% (0/22)	0% (0/22)

Conclusions

Clinicians should be aware of the risk of heparin-induced thrombocytopenia when prescribing heparin, including low molecular weight heparin and unfractionated heparin. The introduction of a simple monitoring protocol will facilitate its prevention. This should include:

- All patients who receive heparin (of any sort) should have a platelet count on day one of starting treatment
- All medical and surgical patients receiving low molecular weight heparin should have platelet counts every 2–4 days from days 4–14 while on treatment.
- If platelet counts drop by 50% or below normal lab limits consider the possibility of heparin-induced thrombocytopenia, stop heparin and inform the haematologist.

If heparin-induced thrombocytopenia is suspected it is essential to withdraw heparin and start an alternative anticoagulant treatment to prevent thromboses. BJHM

Conflict of interest: none.

Antonelli D, Fares L, Anene C (2000) Enoxaparin associated with hugh abdominal wall hematomas: a report of two cases. *Am Surg* **66**(8): 797–800

Baglin T, Barrowcliffe TW, Cohen A, Greaves M (2006) Guidelines on the use and monitoring of heparin. *Br J Haematol* **133**(1): 19–34

Bickler P, Brandes J, Lee M, Bozic K, Chesbro B, Claassen J (2006) Bleeding complications from femoral and sciatic nerve catheters in patients receiving low molecular weight heparin. *Anesth Analg* **103**(4): 1036–7

Burgess JK, Lindeman R, Chesterman CN, Chong BH (1995) Single amino acid mutation of Fc gamma receptor is associated with the development of heparin-induced thrombocytopenia. *Br J Haematol* **91**(3): 761–6

Chong BH (1995) Heparin-induced thrombocytopenia. *Br J Haematol* **89**(3): 431–9

Dickinson LD, Miller LD, Patel CP, Gupta SK (1998) Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* **43**(5): 1074–81

Farner B, Eichler P, Kroll H, Greinacher A (2001) A comparison of danaparoid and lepirudin in heparin-induced thrombocytopenia. *Thromb Haemost* **85**(6): 950–7

Houde JP, Steinberg G (1999) Intrahepatic hemorrhage after use of low-molecular-weight heparin for total hip arthroplasty. *J Arthroplasty* **14**(3): 372–4

Imberti D, Ageno W, Dentali F, Giorgi Pierfranceschi M, Croci E, Garcia D (2006) Management of primary care patients with suspected deep vein thrombosis: use of a therapeutic dose of low-molecular-weight heparin to avoid urgent ultrasonographic evaluation. *J Thromb Haemost* **4**(5): 1037–41

Joint Formulary Committee (2006) Parenteral anticoagulants. In: *British National Formulary* [51]. British Medical Association and Royal Pharmaceutical Society of Great Britain, London: 119–22

King DJ, Kelton JG (1984) Heparin-associated thrombocytopenia. *Ann Intern Med* **100**(4): 535–40

Leyvraz PF, Bachmann F, Hoek J, Büller HR, Postel M, Samama M, Vandenbroek MD (1991) Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *BMJ* **303**(6802): 543–8

Lilikakis AK, Papapolychroniou T, Macheras G, Michelinakis E (2006) Thrombocytopenia and intra-cerebral complications associated with low-molecular-weight heparin treatment in patients undergoing total hip replacement. A report of two cases. *J Bone Joint Surg Am* **88**(3): 634–8

Mohr DN, Silverstein MD, Murtaugh PA, Harrison JM (1993) Prophylactic agents for venous thrombosis in elective hip surgery. Meta-analysis of studies using venographic assessment. *Arch Intern Med* **153**(19): 2221–8

Shaieb MD, Watson BN, Atkinson RE (1999) Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis. *J Arthroplasty* **14**(4): 432–8

Stern SH, Wixson RL, O'Connor D (2000) Evaluation of the safety and efficacy of enoxaparin and warfarin for prevention of deep vein thrombosis after total knee arthroplasty. *J Arthroplasty* **15**(2): 153–8

Warkentin TE (1999) Heparin-induced thrombocytopenia: a clinicopathologic syndrome. *Thromb Haemost* **82**(2): 439–47

Warkentin TE, Heddle NM (2003) Laboratory diagnosis of immune heparin-induced thrombocytopenia. *Curr Hematol Rep* **2**(2): 148–57

Wolf H (1994) Low-molecular-weight heparin. *Med Clin North Am* **78**(3): 733–43

KEY POINTS

- There is little awareness of heparin-induced thrombocytopenia – a potentially fatal complication of heparin use.
- All patients prescribed heparin should have regular full blood counts to monitor for thrombocytopenia until at least day 14.
- Thrombocytopenia should trigger the cessation of heparin and immediate consultation with a haematologist.