Managing heparin infusions

Introduction

Heparin is well recognized for the treatment and prophylaxis of venous thrombo-embolism, and for use in acute coronary syndromes. Use of unfractionated heparin has largely been superseded by low molecular weight heparins, factor Xa inhibitors, and direct thrombin antagonists, as a result of their ease of administration and improved side-effect profile. However, intravenous and subcutaneous unfractionated heparin remains useful in particular clinical scenarios such as renal failure or when there is a significant risk of bleeding. Its infrequent use means that clinicians are often unfamiliar with how to manage patients receiving unfractionated heparin. This article gives practical advice on using unfractionated heparin including the management of dosing and adverse effects.

Pharmacology

Heparin is a naturally occurring glycosaminoglycan produced by mast cells and is pharmaceutically extracted from porcine mucosa. The molecular weight of unfractionated heparin ranges from 3–30 kDa, while low molecular weight heparins are less than 5 kDa (Hirsh et al, 2001; Baglin et al, 2006).

The anticoagulant properties of heparin derive from the presence of a specific pentasaccharide sequence of non-sulphated uronic acid that binds with high affinity to antithrombin and potentiates its activity (Lindahl et al, 1979). This pentasaccharide sequence (1.7 kDa) confers anti-factor-Xa activity, but anti-IIa activity (and thus activated partial thromboplastin time prolongation) requires a chain length of at least 18 saccharides (5.4 kDa) to bridge thrombin and antithrombin. Thus low molecular weight heparin does not cause activated partial thromboplastin time prolongation (Lane et al, 1984; Hirsh et al, 2001). Thrombin inhibition prevents fibrin formation and also inhibits thrombin-induced activation of platelets, factor V and factor VII (*Figure 1*) (Hirsh et al, 2001).

When given intravenously unfractionated heparin has an immediate effect, with a half-life of 30–120 minutes; administered subcutaneously its onset is delayed by 2 hours, but has a half-life of approximately 10 hours (Scottish Intercollegiate Guidelines Network, 2009).

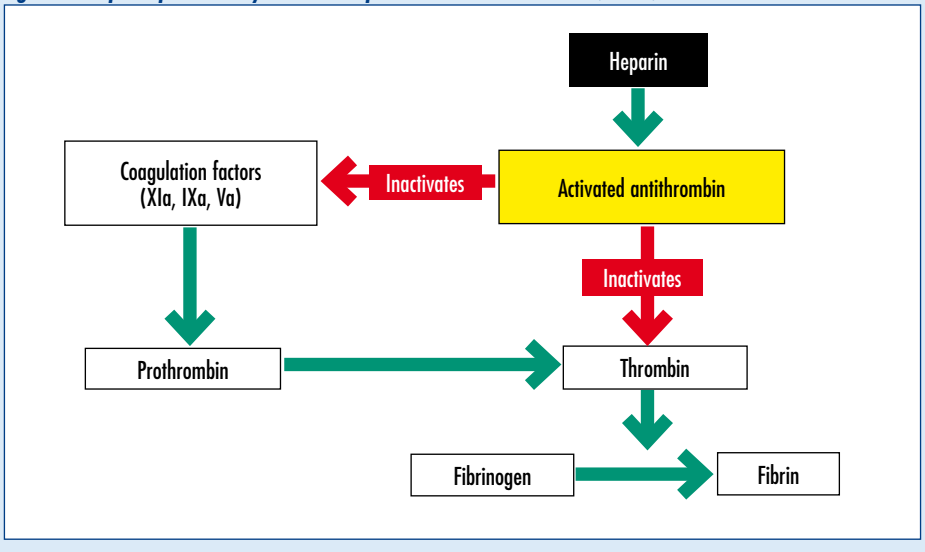
The ten-fold intersubject variability in response to heparin derives from its property of binding to antithrombin-independent positively charged surfaces including plasma proteins, proteins released from platelets and endothelial cells. 'Heparin resistance' may result from this variability, and is defined if over 35 000 units per day are required to maintain a therapeutic activated partial thromboplastin time (Anderson and Saenko, 2002). Metabolism is by two mechanisms: a saturable mechanism with binding to macrophages and endothelial cells, with clearance by the reticuloendothelial system; and a non-saturable mechanism with renal clearance (Hirsh et al, 2001; Scottish Intercollegiate Guidelines Network, 2009). There is no evidence that heparin crosses the placenta and is preferable to warfarin in this regard.

Indications

Heparins are indicated in the prevention and treatment of venous thromboembolism, acute coronary syndromes, acute critical limb ischaemia, carotid endarterectomy, haemodialysis, and the prevention of mural thrombus after myocardial infarction (Scottish Intercollegiate Guidelines Network, 2009). Owing to ease of administration and improved side-effect profiles, accepted practice is now to use low molecular weight heparin, factor Xa inhibitors or direct thrombin antagonists.

When determining appropriate anticoagulation, clinicians should consider the patient's intrinsic haemostatic potential (patient risk), the risk of thrombosis or bleeding associated with the condition of the patient (disorder risk), and the efficacy and risk of bleeding with anticoagulation (heparin risk) (Baglin et al, 2006). The primary use for unfractionated heparin is in patients with a high risk of bleeding. The short half-life and the availability of a full antidote to unfractionated heparin, compared with low molecular weight heparin, means that in these patients unfractionated heparin allows an improved balance between therapeutic anticoagulation and risk of haemorrhage.

Figure 1. Heparin pharmacodynamics. Adapted from Hoffbrand et al (2006).



Dr Nicholas F Brown *is FY2, Watford General Hospital, West Hertfordshire Hospitals NHS Trust, Watford, Herts WD18 0HB,* **Dr Emily Bart-Smith** *is Haematology Registrar and* **Dr Donald Gillett** *is Consultant Haematologist, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, Kent*

Correspondence to: Dr NF Brown (n.brown4@nhs.net)

Use of unfractionated heparin should be considered in the following situations:

- If the creatinine clearance is less than 30 ml/min or this degree of renal impairment is suspected (Baglin et al, 2006).
- Myocardial infarction patients at high risk of systemic emboli or venous thromboembolism (anterior Q wave infarction, severe left ventricular dysfunction, congestive cardiac failure, prior history of venous thromboembolism) should have unfractionated heparin for 48 hours, and then continue with therapeutic dose unfractionated heparin or low molecular weight heparin thereafter (Baglin et al, 2006).
- In disseminated intravascular coagulation heparins are generally not used, but in the following causes of disseminated intravascular coagulation unfractionated heparin may be considered, typically used in low doses: retained dead fetus syndrome, giant haemangioma, solid tumour, acute promyelocytic leukaemia (rarely given the widespread availability of all-trans retinoic acid) (Baglin et al, 2006).
- Where rapid reversal of anticoagulation by protamine sulphate is required (e.g. surgical patients or late pregnancy).

Relative contraindications to the use of heparin include haemophilia, haemorrhagic disorders, thrombocytopenia (platelet count $<80x10^9$/litre), history of heparin-induced thrombocytopenia, recent cerebral haemorrhage, severe hypertension, peptic ulcer, major trauma, recent eye or nervous system surgery, acute bacterial endocarditis, hypersensitivity to heparin, and spinal or epidural anaesthesia (Baglin et al, 2006; Joint Formulary Committee, 2011).

Dosing and monitoring

In the UK, unfractionated heparin is assayed in international units (IU), as defined by the World Health Organization International Standard (Baglin et al, 2006). Low dose subcutaneous unfractionated heparin may be used for thromboprophylaxis: 5000 IU administered 8-hourly, or 7500 IU 12-hourly, and 2 hours before surgery (Joint Formulary Committee, 2011). Monitoring of activated partial thromboplastin time is not routinely required unless pregnant, in extremes of body weight, if adverse events occur, or in severe renal impairment (Scottish Intercollegiate Guidelines Network, 2010).

In the treatment of venous thromboembolism, acute coronary syndrome and acute peripheral artery occlusion, a loading dose of 5000 IU or 75 IU/kg should be administered intravenously, and then a continuous intravenous infusion of 15 000 IU or 18 IU/kg/hr. Owing to the very short half-life of unfractionated heparin, even a short interruption of the infusion will result in normalization of the activated partial thromboplastin time. The importance of continuous infusion should therefore be stressed to nursing staff. Alternatively an initial loading dose may be given, with an equivalent daily dose given twice daily subcutaneously (Baglin et al, 2006). For dosing in other clinical scenarios, refer to the *British National Formulary* (Joint Formulary Committee, 2011).

After initiating a heparin infusion, subsequent dosing depends on the patient's response to unfractionated heparin, which is determined by monitoring the activated partial thromboplastin time. Owing to lack of standardization of activated partial thromboplastin time between laboratories, each laboratory has its own standardized target range for the activated partial thromboplastin time. Thus a target ratio of the patient's current activated partial thromboplastin time compared with a 'control' activated partial thromboplastin time is used, with a desired ratio of 1.5–2.5 in venous thromboembolism and acute coronary syndrome management. The 'control' activated partial thromboplastin time can be either the patient's baseline activated partial thromboplastin time before heparin initiation, or the mid-point of the laboratory's reference range (Baglin et al, 2006). Typically, the patient's baseline activated partial thromboplastin time is used, as the inter-patient variation in response to heparin can be partly attributed to variations in baseline activated partial thromboplastin time.

The activated partial thromboplastin time should be measured 4 hours after starting an infusion. The activated partial thromboplastin time ratio can then be determined and the dosing adjusted as needed. Thereafter, the activated partial thromboplastin time ratio should be determined 4 hours after every dose change, and then every 24 hours. Once two activated partial thromboplastin times 24 hours apart are within the therapeutic range, the patient can be considered stable, and activated partial thromboplastin times should be measured daily (Scottish Intercollegiate Guidelines Network, 2010). The activated partial thromboplastin time response to changes in heparin infusion rates is not always linear, and so heparin dosing should be adjusted cautiously, in increments of 100–200 IU/hr. However, if the activated partial thromboplastin time is normal or low, an additional loading dose is recommended.

Before initiating treatment, a baseline haemoglobin, platelet count, coagulation screen, urea, electrolytes and liver function tests should be checked in order to rule out contraindications and determine bleeding risk (Scottish Intercollegiate Guidelines Network, 2009). As well as monitoring the activated partial thromboplastin time, the platelet count should be monitored every 2–4 days in all heparin-naive patients from day 4 to 14 of heparin treatment, and from day 1 to 14 in patients who have received any form of heparin in the prior 100 days, to monitor for heparin-induced thrombocytopenia (Keeling et al, 2006). Serum potassium should be monitored in patients receiving heparin for more than 1 week to monitor for heparin-induced aldosterone deficiency (Joint Formulary Committee, 2011).

Side effects and managing adverse events

Haemorrhage

Haemorrhage is a predictable side effect of heparin use, and the risk is dose-dependent. The concomitant use of non-steroidal anti-inflammatory drugs and antiplatelets should be rationalized, and intramuscular injections should be avoided. Owing to the short half-life of unfractionated heparin, minor bleeding can be managed simply by discontinuing the heparin infusion, and monitoring the patient's observations, activated partial thromboplastin time, haemoglobin and platelet count.

With major bleeding, if rapid reversal is required, protamine sulphate can be used as a specific antidote. Protamine dosing is

determined by heparin dose. Protamine 1 mg neutralizes 80–100 units of heparin when given within 15 minutes of heparin. A lower dose is required if given more than 15 minutes after the heparin is stopped. Owing to the risk of severe anaphylactoid reactions, protamine should only be used with severe bleeding. This risk is increased in patients who have had previous treatment with protamine or protamine insulin, have a fish allergy, and in men who are infertile or who have had a vasectomy (Joint Formulary Committee, 2011).

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a notable adverse effect of heparin as a result of a 20–40-fold increased risk (odds ratio) of arterial and venous thrombosis (heparin-induced thrombocytopenia thrombosis) (Warkentin and Greinacher, 2004). Type 1 heparin-induced thrombocytopenia presents within 2 days of starting heparin, and the platelet count normalizes with continued therapy. It is a non-immune disorder, and occurs as a result of the direct effect of heparin on platelet activation.

Type 2 heparin-induced thrombocytopenia is an immune-mediated reaction that typically develops 5–10 days (rarely up to 14 days) after starting heparin, although may occur within 24 hours of re-exposure in a patient who has received any form of heparin in the preceding 100 days. It can present with an incidental fall in platelet count of over 50% or to below the normal reference range (90% of patients with heparin-induced thrombocytopenia; rarely falls below $15x10^9$/litre), arterial or venous thrombosis, skin lesions, or a generalized systemic reaction (Warkentin and Greinacher, 2004; Scottish Intercollegiate Guidelines Network, 2010).

Type 2 heparin-induced thrombocytopenia occurs in 0.5% of medical patients treated with unfractionated heparin, but in up to 5% of orthopaedic surgery patients (Chong and Isaacs, 2009). It is a hypersensitivity reaction, mediated by an IgG antibody that reacts with the platelet factor 4/heparin complex, and binds to and induces platelet activation, causing aggregation and thrombus formation. Heparin-induced thrombocytopenia antibodies additionally activate endothelial cells and monocytes, further inducing thrombin generation and fibrin thrombus formation (*Figure 2*) (Chong and Isaacs, 2009).

Diagnosis can be confirmed with platelet activation assays, platelet aggregation assays, or by testing for IgG to platelet factor 4, in which it is pertinent to know whether the antibody is present, but also its optical density and its inhibition by heparin.

Before confirming a diagnosis of heparin-induced thrombocytopenia with laboratory tests, a pre-test probability of heparin-induced thrombocytopenia should be determined and used to guide management. One scoring system (*Table 1*) uses the '4 Ts': level of thrombocytopenia, timing of onset of platelet fall, thrombosis or other sequelae, and other cause of platelet fall, in order to stratify the pre-test risk of heparin-induced thrombocytopenia into low, moderate or high (Warkentin et al, 2003).

If the pre-test probability is high, heparin should be stopped and alternative anticoagulation started while lab tests are performed. If the probability is low heparin can be continued; if the probability is moderate clinician judgement should be used (Keeling et al, 2006).

In a patient with confirmed or a high probability of heparin-induced thrombocytopenia, heparin should be immediately stopped and the patient should be started on therapeutic dose lepirudin (a direct thrombin inhibitor) or danaparoid (factor

Figure 2. Mechanism of heparin-induced thrombocytopaenia. α-granules release platelet factor 4 (PF4) which form a complex with heparin on the platelet surface. IgG forms against this complex and activates the platelet through Ig receptor Fc-γRII causing platelet stimulation, further release of PF4, thrombus formation, and thrombocytopenia. Adapted from Hoffbrand et al (2006).

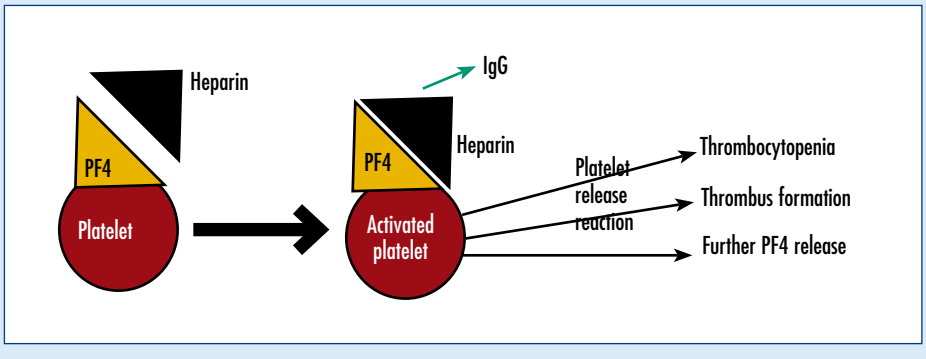


Table 1. A scoring system to estimate the pre-test probability of heparin-induced thrombocytopenia

	Points (maximum score = 8)		
	2	**1**	**0**
Thrombocytopenia	>50% platelet fall, or nadir 20–100x10^9/litre	30–50% platelet fall, or nadir 10–19x10^9/litre	<30% platelet fall, or nadir <10x10^9/litre
Timing of onset platelet fall	Days 5–10 or ≤1 with heparin exposure within past 100 days	>day 10 or timing unclear (but fits with heparin-induced thrombocytopenia)	≤1 day (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis or acute systemic reaction following intravenous heparin bolus	Progressive, recurrent or silent thrombosis, erythematous skin lesions	None
Other cause of platelet fall	None evident	Possible	Definite

0–3 = low probability, 4–5 = moderate probability, 6–8 = high probability. From Warkentin et al (2003)

Xa inhibitor) (Keeling et al, 2006). Specialist advice should be sought. Between 23 and 52% of diagnoses with isolated heparin-induced thrombocytopenia (i.e. without thrombosis) subsequently develop symptomatic thrombosis, which should be screened for with lower leg Doppler ultrasound, 5% develop disseminated intravascular coagulation, and 4.3–4.8% die from thrombosis (Warkentin and Greinacher, 2004; Keeling et al, 2006). Warfarin should be avoided until the platelet count has recovered because of high rates of skin necrosis (Warkentin and Greinacher, 2004).

Other side effects

Other side effects of heparins include osteoporosis, particularly in pregnant women, as a result of decreased osteoblast and increased osteoclast activity (Baglin et al, 2006). Hyperkalaemia can occur as a result of inhibition of aldosterone secretion, and is particularly found in those with additional risk factors including diabetes mellitus, chronic renal failure and acidosis. The risk increases with prolonged use, and serum potassium should be measured before starting heparin, and regularly if continued for more than 1 week (Joint Formulary Committee, 2011). Uncommon adverse effects include rebound hyperlipidaemia following heparin withdrawal, priapism, alopecia, skin necrosis and hypersensitivity reactions (Joint Formulary Committee, 2011).

Conclusions

Unfractionated heparin has been superseded by low molecular weight heparins in the routine management of venous thromboembolism and acute coronary syndrome, but remains important in the management of specific groups, notably patients with renal failure or a high risk of bleeding. Patient response to heparin is variable, and thus the activated partial thromboplastin time must be monitored regularly, with dosing adjusted accordingly.

Haemorrhage caused by heparin is managed by stopping the heparin infusion, and with protamine sulphate if severe. Patients on heparin should be monitored with regular platelet counts for signs of heparin-induced thrombocytopenia, which carries a significant risk of thrombosis. If suspected, a pre-test probability should be calculated while laboratory investigations are ordered, and if the risk is high heparin should be stopped and alternative anticoagulation started. BJHM

Conflict of interest: none.

KEY POINTS

- Although largely superseded by low molecular weight heparins, unfractionated heparin still has a role in anticoagulation, particularly in patients with renal failure or with a high risk of bleeding.
- Dosing is patient-specific and is tailored to an activated partial thromboplastin time taken 4 hours after an infusion is commenced and after any dose changes; once stabilized the activated partial thromboplastin time is monitored daily.
- Patients on heparin should be monitored with frequent platelet counts for heparin-induced thrombocytopenia, which carries a significant risk of thrombosis.
- In patients with suspected heparin-induced thrombocytopenia, a pre-test probability of heparin-induced thrombocytopenia should be determined and if the risk is deemed high, heparin should be stopped and alternative anticoagulation started.
- Haemorrhage should be managed by stopping the heparin infusion, and in severe cases protamine sulphate may be used as an antidote.

TOP TIPS

- Determine a target activated partial thromboplastin time ratio, typically 1.5–2.5 of the patient's baseline activated partial thromboplastin time.
- Commence the infusion with a loading dose of 5000 IU or 75 IU/kg given intravenously, followed by a continuous infusion of 15000 IU/hr or 18 IU/kg/hr.
- Measure the activated partial thromboplastin time and determine the activated partial thromboplastin time ratio 4 hours after starting or any dose change, and then daily once the ratio is in range.
- If required adjust the dosage cautiously in increments of 100–200 IU/hr, considering a further loading dose if still within the normal range.

Anderson JA, Saenko EL (2002) Heparin resistance. *Br J Anaesth* **88:** 467–9

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

Chong B, Isaacs A (2009) Heparin-induced thrombocytopenia: What clinicians need to know. *Thromb Haemost* **101:** 279–83

Hirsh J, Anand SS, Halperin JL, Fuster V (2001) Mechanism of action and pharmacology of unfractionated heparin. *Arterioscler Thromb Vasc Biol* **21:** 1094–6

Hoffbrand AV, Moss PAV, Pettit JE (2006) *Essential Haematology.* 5th edn. Blackwell Publishing, Oxford

Joint Formulary Committee (2011) *British National Formulary.* 62 edn. BMJ Group and Pharmaceutical Press, London

Keeling D, Davidson S, Watson H (2006) Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin-induced thrombocytopenia. *Br J Haematol* **133**(3): 259–69

Lane DA, Denton J, Flynn AM, Thunberg L, Lindahl U (1984) Anticoagulant activities of heparin oligosaccharides and their neutralisation by platelet factor 4. *Biochem J* **218:** 725–32

Lindahl U, Backstrom G, Hook M, Thunberg L, Fransson LA, Linker A (1979) Structure of the antithrombin-binding site in heparin. *Proc Nat Acad Sci USA* **76:** 3198–202

Scottish Intercollegiate Guidelines Network (2009) *Antithrombotic Therapy.* Scottish Intercollegiate Guidelines Network, Edinburgh

Scottish Intercollegiate Guidelines Network (2010) *Prevention and management of venous thromboembolism.* A national clinical guideline. Scottish Intercollegiate Guidelines Network, Edinburgh

Warkentin TE, Greinacher A (2004) Heparin-induced Thrombocytopenia: Recognition, Treatment, and Prevention. *Chest* **126:** 311S–337S

Warkentin TE, Aird WC, Rand JH (2003) Platelet-Endothelial Interactions: Sepsis, HIT, and Antiphospholipid Syndrome Hematology. *Am Soc Hematol Educ Program*: 497–519