Heparins for venous thromboembolism prophylaxis – safety issues

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Summary

Heparins are commonly used to prevent venous thromboembolism. Although they are effective anticoagulants, heparins have a high risk of adverse effects if used inappropriately. Safer heparin prescribing is achieved through careful patient selection by assessing the risk of venous thromboembolism. Consider the drugs' contraindications and precautions including renal function, concomitant medication use and spinal needle insertion. Comparative drug information needs to be considered when choosing the optimal heparin for an individual patient. The timing of perioperative heparin administration depends on the choice of heparin, type of surgery and type of anaesthesia. Patients should be carefully monitored during prophylaxis.

Key words: anticoagulant, dalteparin, danaparoid, enoxaparin, fondaparinux.

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Introduction

Heparins are effective anticoagulants and can be used to prevent venous thromboembolism in hospitalised medical and surgical patients. In Australia it has been estimated that the overall prevalence of venous thromboembolism in all hospitalised patients is 2–3 per 1000 admissions.[1] There is therefore growing Australian and international encouragement for prophylaxis, so increased numbers of inpatients will be prescribed a heparin.

'Heparin' or 'heparins' refers to the following medications available in Australia:

- unfractionated heparin
- low molecular weight heparins – dalteparin, enoxaparin
- synthetic selective inhibitor of activated factor X – fondaparinux
- heparinoid – danaparoid.

Although the benefits of using heparin in venous thromboembolism prophylaxis generally outweigh the risks, harm from low-dose heparin can be severe and the risks should not be ignored. While adverse effects are less common with low-dose heparin than with therapeutic doses of heparin, bleeding can still occur if other risk factors for bleeding are present, such as renal impairment or interaction with other drugs. Also, bleeding events can be expected to increase in frequency as the number of patients prescribed heparin for venous thromboembolism prophylaxis continues to increase. For example, a program of mandatory venous thromboembolism prophylaxis with low molecular weight heparin alone or in combination with warfarin has resulted in increased bleeding rates after hip and knee arthroplasty.[2] Incidents with anticoagulants including heparins (at all doses) continue to be commonly reported to incident reporting systems in Australia and the USA.[3,4] Clinicians must consider the patient's safety when prescribing heparin as part of a strategy for venous thromboembolism prophylaxis as discussed in publications such as 'Safe prescribing of heparins for venous thromboembolism prophylaxis: a position statement of the NSW Therapeutic Advisory Group'.[5]

Patients requiring venous thromboembolism prophylaxis

The risk of venous thromboembolism should be assessed in all adult patients before or on admission to hospital. Currently available guidelines differ regarding which patients require venous thromboembolism prophylaxis.[6–12] An Australian guideline for venous thromboembolism prophylaxis is currently under development.[13] Table 1 shows the current recommendations in the USA.[11]

Contraindications and precautions

All patients should be assessed for contraindications and the precautions needed before starting prophylaxis. Absolute contraindications to heparin include known hypersensitivity, past or present heparin-induced thrombocytopenia and active bleeding.

Caution is required when prescribing heparin to patients with conditions that may increase the risk of bleeding (see box). In these patients, the decision to prescribe heparin should be made on an individual basis balancing the relative benefit and harm. Tests for coagulation, such as prothrombin time, are not routinely required.[5]

Renal function

Patients with moderate to severe renal dysfunction have a higher risk of bleeding with some heparins. Assessment of renal function using creatinine clearance is important before

Table 1

Recommendations for thromboembolism prophylaxis [11]*

Indications	Procedure/condition
Surgical procedures generally requiring venous thromboembolism prophylaxis	Acute spinal cord injury Major trauma Major surgery including: - general cancer or non-cancer surgery - hip and knee arthroplasty - open gynaecological surgery - open urological surgery - prolonged surgery†
Surgical procedures generally not requiring venous thromboembolism prophylaxis when no additional risk factors are present	Elective spine surgery Knee arthroscopy Isolated lower extremity injuries Laparoscopic surgery Transurethral surgery Vascular surgery
Medical conditions generally requiring venous thromboembolism prophylaxis	Congestive heart failure Severe respiratory disease Immobility plus: - cancer - previous venous thromboembolism - sepsis - acute neurological disease - inflammatory bowel disease

Mechanical methods of prophylaxis, such as stockings, are recommended in patients at high risk of bleeding.

* These recommendations are based on guidelines from the USA, pending the publication of new Australian guidelines

† Prolonged surgery may increase the risk of venous thromboembolism in patients who are over 40 or who have other risk factors

prescribing low molecular weight heparins or fondaparinux. In patients with a creatinine clearance less than 30 mL/min enoxaparin dosage should be reduced to 20 mg daily and fondaparinux is contraindicated. For danaparoid, dose reductions should be considered when creatinine clearance is under 20 mL/min. Unfractionated heparin can be prescribed without dose alteration.[5]

Interactions

Heparin should be prescribed cautiously in patients taking drugs that can increase bleeding, for example antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs) and thrombolytics. The decision to co-prescribe heparin with these drugs should be made on an individual patient basis in consultation with senior staff and taking into account patient preference. Careful clinical review and monitoring of the patient is recommended. Low-dose aspirin required for prevention or treatment of cardiovascular disease may be continued.

Examples of problems that may increase risks with heparin

Bleeding disorders, e.g. haemophilia

Concomitant use of certain medications, e.g. clopidogrel

Conditions where bleeding would be catastrophic, e.g. focal lesions, haemorrhagic stroke

Creatinine clearance <30 mL/min

High risk of uncontrolled haemorrhage, e.g. acute ulcerative gastrointestinal conditions, anaemia of unknown cause

Recent surgery on eye, brain or spinal cord

Severe thrombocytopenia (platelets <50 x 10^9/L)

Severe liver disease with coagulopathy and/or oesophageal varices

Spinal or epidural needle insertion (spinal tap or spinal anaesthesia)

Unfractionated heparin can raise potassium concentrations. This may lead to hyperkalaemia when co-prescribed with other drugs that increase potassium, for example angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, potassium sparing diuretics, potassium supplements, NSAIDs or trimethoprim. Patients receiving unfractionated heparin for more than three days who are at risk of developing hyperkalaemia should have their potassium monitored at least every four days.[14]

Spinal needle insertion

When heparins are prescribed for patients undergoing spinal needle insertion the risk of an epidural or spinal haematoma is increased. Insertion and removal of needles and catheters should occur when the anticoagulant effect is lowest, generally just before the next dose is due. If bleeding occurs during needle placement, the subsequent dose of heparin should be delayed for 24 hours and the patient should have neurological observations.[15]

Choice of heparin

Different heparins have different harm:benefit ratios, although each carries a similar bleeding risk. There are usually options available for each clinical indication, but heparins are not clinically interchangeable (unit for unit) (Table 2). When choosing a heparin consider the clinical indication, patient factors (for example renal impairment), type of surgery and anaesthesia, dosing schedule, risk of heparin-induced thrombocytopenia, reversibility and cost.[5] Unfractionated heparin is not recommended for prophylaxis in hip or knee arthroplasty or trauma patients.[11]

Timing and duration of heparin administration

Care should be taken to determine the optimal time for giving perioperative heparin.[5] The timing depends on the type and dosing schedule of the heparin chosen and the type of procedure and anaesthesia planned. There is no advantage in

Table 2

Differences between heparins when used for venous thromboembolism prophylaxis [5]

	Unfractionated heparin	Enoxaparin	Dalteparin	Danaparoid	Fondaparinux
Elimination	Liver and reticuloendothelial system	Primarily renal	Primarily renal	Renal	Renal
Dosing in renal impairment	No dosage adjustment required	Reduce dose if CrCl <30 mL/min	Unknown	Consider dose reductions if CrCl <20 mL/min	Do **not** use if CrCl <30 mL/min Use cautiously if CrCl = 30–50 mL/min
Renal function testing	Not required	At baseline	At baseline	Not required	At baseline and periodically. Discontinue in patients who develop labile renal function or severe renal impairment
Incidence of HIT	Highest incidence	Lower incidence	Lower incidence	Can be used to treat HIT	Unknown
Platelet count monitoring at baseline[17]	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Not required	Yes
Ongoing platelet count monitoring[17]	Every 2–4 days in postoperative and medical patients up to 14 days or until heparin is stopped (whichever is earlier)	Every week in postoperative patients up to 14 days or until heparin is stopped (whichever is earlier) Not required in medical or obstetric patients	Every week in postoperative patients up to 14 days or until heparin is stopped (whichever is earlier) Not required in medical or obstetric patients	Not required	When treatment ceased
Other monitoring[17]	Activated partial thromboplastin time testing is not required for prophylactic dosing Assess for bleeding	Assess for bleeding	Assess for bleeding	Functional anti-factor Xa (patients with renal impairment, or those weighing more than 90 kg) Assess for bleeding	Assess for bleeding
Approved indication for VTE prophylaxis	Prevention of VTE in surgical and high risk medical patients	Prevention of VTE in surgical patients and in medical patients bedridden due to acute illness	Prevention of VTE in surgical patients	Prevention of VTE in patients undergoing general or orthopaedic surgery	Prevention of VTE in high-risk orthopaedic surgery (hip fracture, knee or hip replacement) and abdominal surgery
Subcutaneous dose in VTE prophylaxis	5000 units 2–3 times daily depending on risk of VTE	20–40 mg once daily depending on risk of VTE	2500–5000 units once daily depending on risk of VTE	750 anti-factor Xa units twice daily	2.5 mg once daily Use with caution in patients who weigh <50 kg
Reversibility with protamine sulfate	Complete	Incomplete, 60% reversible	Incomplete, 60–75% reversible	Non-reversible	Non-reversible
Daily cost compared to twice-daily UFH		~1.5–2 x cost	~2 x cost	~15 x cost	~4 x cost

Refer to guidelines for the preferred heparin for each clinical indication[11]

VTE venous thromboembolism
CrCl creatinine clearance
UFH unfractionated heparin
HIT heparin-induced thrombocytopenia

starting venous thromboembolism prophylaxis preoperatively rather than postoperatively.[11] In patients undergoing neurosurgery, heparin, if indicated, should never be started preoperatively. After trauma, patients should not be started on heparin until primary haemostasis is established.[11]

Heparin should be continued while patients remain at increased risk of developing venous thromboembolism – up to 35 days postoperatively in some orthopaedic patients.[11]

Patient monitoring

While routine clotting studies are not required during prophylaxis, patients need to be assessed for bleeding. Unless they are taking danaparoid, patients will need platelet counts every few days.

Bleeding

Easy bruising and petechial haemorrhages may precede frank bleeding. Nose bleeds, haematuria or melaena may be the first sign of bleeding, so check for these signs.[5] Bleeding can often be controlled by stopping the heparin. In some patients protamine sulfate may be considered for heparin reversal, however it does not reverse the effects of danaparoid and fondaparinux (Table 2). Patients with bleeding should undergo fluid management and resuscitation as required.

Thrombocytopenia

Unfractionated heparin, and to a lesser extent low molecular weight heparins, may cause heparin-induced thrombocytopenia. A diagnosis of heparin-induced thrombocytopenia requires the presence of antibodies (heparin-dependent platelet antibodies) and one of the following events:[17]

- unexplained platelet count fall of 30–50% from baseline
- venous or arterial thrombosis
- skin lesions at heparin injection sites
- systemic anaphylactoid reactions.

Heparin-induced thrombocytopenia usually occurs 4–10 days (sometimes weeks) after starting heparin (earlier in patients exposed to heparin in the previous three months). Management requires cessation of heparin and alternative anticoagulation (danaparoid or lepirudin). Low molecular weight heparins should not be used in patients who have a history of heparin-induced thrombocytopenia with unfractionated heparin.

A milder, reversible thrombocytopenia may also develop. In these cases antibodies are not present. If the platelet count remains greater than 100 x 10^9/L, heparin may be continued.[17]

Platelet counts should be measured intermittently in patients prescribed unfractionated heparin or low molecular weight heparins, and at baseline in patients prescribed fondaparinux, but are not required in patients prescribed danaparoid.[17] Recommendations for platelet count monitoring vary depending on the type of patient and the choice of heparin (Table 2).[16,17]

Future directions

The forthcoming Australian guidelines will clarify the indications for thromboembolism prophylaxis[13], however practice may soon have to change. Dabigatran and rivaroxaban have recently been approved for use in Australia. As these anticoagulants can be given orally, they may supersede heparins in some indications.

Conclusion

Heparin is an effective but high-risk drug that can cause bleeding even in low doses. Safer heparin prescribing can be achieved through careful patient selection taking into consideration the clinical indication for venous thromboembolism prophylaxis, contraindications and precautions. Heparin choice should be matched to the individual patient's requirements. Patients should be monitored for bleeding while heparin administration is continued.

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Note: URLs are available at www.australianprescriber.com

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New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Dutasteride

Avodart (GlaxoSmithKline)

500 microgram capsules

Approved indication: benign prostatic hyperplasia

Australian Medicines Handbook section 13.2.2

Although surgery is the definitive treatment for benign prostatic hyperplasia, some patients can be managed with drugs (see 'Drug treatment of benign prostatic hypertrophy', Aust Prescr 1995;18:30–2). The drug treatments include finasteride which inhibits the conversion of testosterone to dihydrotestosterone. This androgen is thought to be responsible for stimulating the growth of the prostate.

Like finasteride, dutasteride is a 5-alpha reductase inhibitor. Finasteride mainly inhibits the type II enzyme found in the prostate, while dutasteride also inhibits the type I enzyme found in the liver and skin. After two weeks of treatment with dutasteride there is a reduction of up to 90% in the concentration of dihydrotestosterone.

The bioavailability of the drug varies from 40% to 94% and it is extensively metabolised. Although cytochrome P450 3A4 is involved in the metabolism, few specific studies of interactions have been carried out in patients. There is a potential for interactions with other drugs metabolised by this enzyme. Most of the metabolites are excreted in the faeces. The half-life of the drug is up to five weeks so it remains in the body for several months after treatment stops. The onset of the full treatment effect is also slow.

In placebo-controlled clinical trials the efficacy of dutasteride has been evaluated using symptom scores in 4325 men. At the start of the studies the average score was 17/35. After two years of treatment this score was significantly reduced by 4.5 points. Dutasteride significantly reduced the volume of the prostate gland. It also significantly improved the urinary flow rate and reduced the risk of acute urinary retention.[1] These effects continued during a two-year open-label extension of the trials.[2]

Dutasteride has adverse effects on sexual function. Patients may develop a decreased libido, ejaculation disorders or impotence. Serum testosterone may increase, but prostate specific antigen concentrations will be reduced by dutasteride.

As dutasteride may affect the development of a male fetus the capsules should not be handled by pregnant women.

Like finasteride (see 'The price of urine', Aust Prescr 1995;18:26–7), the effect of dutasteride is modest. A placebo can improve a patient's symptom score by 2.3 points and the statistically significant change in urinary flow rate is only 1.3 mL/second greater than placebo.[1] Drug treatment should therefore only be used if self-management strategies do not work.

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