Enoxaparin

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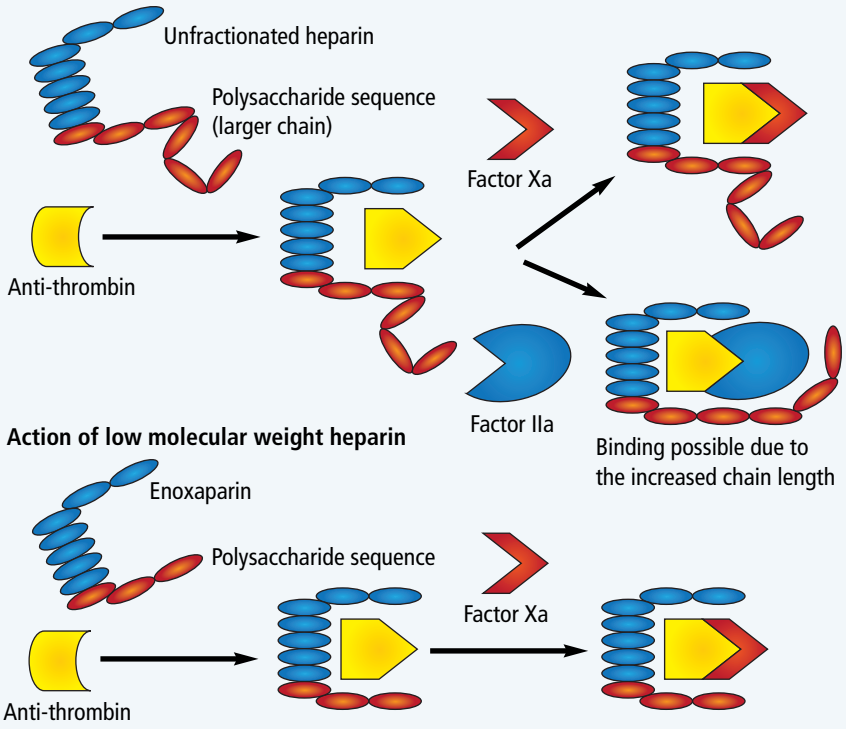

NOTES. Factor Xa inhibition is accelerated by the structural change of anti-thrombin following pentasaccharide binding of the heparin molecule. In comparison the inhibition of factor IIa by the heparin-anti-thrombin complex requires the further formation of a tertiary structure, comprising of all three molecular units. Only heparin chains with the sufficient length of polysaccharide units are physically capable of creating this structure therefore this is less a feature of the mechanism of action of enoxaparin.

Figure 1. The pharmacological action of enoxaparin compared to unfractionated heparin

Introduction

Diabetes is a proinflammatory and prothrombotic condition. The development of type 2 diabetes is strongly associated with obesity which is an independent risk factor for the development of venous thromboembolism (VTE). In combination with an acute medical illness requiring hospital admission it is particularly important to consider thromboprophylaxis in this patient cohort because of the increased risk.

The use of low molecular weight heparin (LMWH) for the prevention of VTE in surgical patients has an extensive and well-established evidence base, but this is not readily extrapolated to patients admitted with a medical illness. Although it is now well recognised that patients admitted acutely unwell with a medical illness may benefit from thromboprophylaxis, more research is required to ensure that appropriate patients get this treatment. National and international guidelines recommend the use of LMWH specifically in medical patients after careful evaluation of risk of VTE. Of the three LMWHs available to the prescriber, only enoxaparin and dalteparin are licensed for prophylaxis of VTE in medical patients. Unfractionated heparin (UFH) is also licensed for this indication.

Clinical pharmacology

Figure 1 outlines the pharmacological action of enoxaparin compared to UFH. Enoxaparin is formed by the chemical/enzymatic depolymerisation of UFH. Enoxaparin chains have an average molecular weight of 4500 Daltons. In comparison, UFH is a more heterogeneous combination of polysaccharide chains with an average weight of 15 000 Daltons (range 3000–30 000). Heparins act as indirect

thrombin inhibitors by binding with anti-thrombin and producing a conformational change to its molecular structure. *In vivo* anti-thrombin primarily acts as an inhibitor of both factors IIa (thrombin) and Xa. Only a minority of the heparin molecules contains the sequence able to interact with anti-thrombin described as the pentasaccharide chain. This is true of both UFH and LMWH. Enoxaparin, in common with the other LMWHs, has significantly more inhibitory activity on factor Xa than IIa. UFH on the other hand has been demonstrated to equally inhibit these factors. This clinically relevant difference results from the total length of the polysaccharide heparin chain.

Enoxaparin has reduced binding to plasma proteins, macrophages and endothelial cells in comparison to UFH. This gives it a more predictable dose-response relationship and longer plasma half-life for a given dose.

Enoxaparin is administered as a subcutaneous injection with dosage and frequency dictated by clinical indication. The standard dose for medical patient prophylaxis of VTE is currently 40mg daily. It is rapidly absorbed with peak plasma activity after 3 hours. It is primarily metabolised in the liver and excreted by the kidneys with a recommended reduction in dose if eGFR is <30ml/min/1.73m^2.

Trials of safety and efficacy

A Cochrane review (updated in 2014) included 16 studies (n=34 369 patients) evaluating the use of heparin or LMWH in the prevention of VTE in acutely ill medical patients (excluding those presenting with acute stroke/myocardial infarction).[1] Three of the six studies looking at LMWH as the active treatment against placebo and three of the six studies comparing LMWH with UFH used enoxaparin. Active treatment with either UFH or LMWH vs placebo was found to significantly decrease the risk of deep vein thrombosis (DVT) in intervention groups across seven studies (OR 0.41; 95% CI 0.25–0.67; p=0.0004). Comparison of UFH to LMWH across six studies with regard to reduced risk of DVT reported a statistically significant decrease in incidence in the LMWH treatment group (OR 0.77; 95% CI 0.62–0.96; p=0.02).

The review did not identify a statistically significant reduction in fatal (six trials) and non-fatal (six trials) pulmonary embolism in medical patients receiving heparin therapy vs placebo. They did, however, report a borderline reduction when combining the two groups across nine studies (OR 0.66; 95% CI 0.43–1.02; p=0.06) with no significant difference between LMWH and UFH across all groups.

The rate of haemorrhage in medical patients receiving heparin prophylaxis is increased across all groups (OR 1.81; 95% CI 1.10–2.98; p=0.02). However, LMWH was shown to have statistically lower rates of major bleeding than UFH (OR 0.43; 95% CI 0.22–0.83; p=0.01).

The Cochrane review results are partly in keeping with the findings reported in previously published meta-analyses with all three providing evidence that thromboprophylaxis with heparin (UFH and LMWH) significantly reduced risk of DVT.[2–4] However, none demonstrated statistically significant difference in reduction of VTE between UFH and LMWH. There was also no reduction in bleeding rates.

Specific evidence for use in diabetes

There are no trials that we are aware of specifically assessing the use of LMWH including enoxaparin in the prevention of DVT in patients with diabetes. In the trials included in the Cochrane review it is likely that many patients had diabetes, particularly in those trials using raised BMI as an inclusion criteria. However, in a population-based study of 2488 consecutive patients with validated VTE, of 476 (19.1%) who had a clinical history of diabetes >33% had thromboprophylaxis omitted having been hospitalised for non-VTE-related illness or had undergone major surgery within three months before diagnosis.[5] Patients with diabetes were more likely than patients without diabetes to suffer recurrent DVTs (14.9% vs 10.7%) and long-term major bleeding complications (16.4% vs 11.7%); all p=0.01.

Discussion

Enoxaparin is a safe and well tolerated medication used on a daily basis in surgical and medical inpatients deemed at risk of VTE. It is one of two LMWHs with the licensed indication for prevention of VTE in acutely ill medical patients, with enoxaparin most extensively studied in this setting. UFH is also licensed for this indication but LMWHs have been adopted in national guidelines in the prevention of VTE in medical patients because of the clinical advantages which include predictability of response, dose-dependent plasma levels, increased half-life and reduction in haemorrhagic complications.

Investigation of novel anticoagulants for thromboprophylaxis in medical patients is currently in progress. Rivaroxaban was shown to be non-inferior to enoxaparin in the prevention of VTE during hospital inpatient stay but at an increased risk of significant haemorrhage.[6] It is likely that thromboprophylaxis in acutely unwell medical patients will remain an important and evolving area with the introduction of newer anticoagulants, but although LMWHs remain the first choice there is still a need for further research including how best to evaluate the risk and treat patients admitted with acute medical illness. This includes patients with diabetes irrespective of whether admission is due directly to a complication of diabetes.

Key points

- Heparin prophylaxis of VTE in medical patients has an established evidence base supporting its use in clinical practice, including its use in patients with diabetes
- The clinical advantages of LMWH vs UFH include predictability, dose-dependent plasma levels, a long half-life and less bleeding for a given anti-thrombotic effect
- Enoxaparin is the most extensively studied LMWH for thromboprophylaxis and should be considered for use in all patients, including those with diabetes, admitted with an acute medial illness unless contraindicated

Declaration of interests

Professor McKay has received honoraria for talks, advisory boards and consultancy work from Sanofi.

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