EDITORIAL

Up close and personal with low-molecular-weight heparins (LMWHs)

S. Lugthart

Department of Haematology, Erasmus MC, Rotterdam, the Netherlands,
email: s.lugthart@erasmusmc.nl

The fundamental purpose of anticoagulants is to provide the clinician with an essential pharmacological method of treating venous thrombosis. The complications associated with thrombosis can have catastrophic effects, such as severe pulmonary embolism or cerebral vascular accidents. Therefore, the significance of anticoagulants in preventing thrombosis cannot be underestimated.

In the Netherlands it is estimated that 1.8 per 1000 patients annually will be diagnosed with a form of thrombosis. The incidence is increased in older patients (over 75 years) to 6.5 per 1000 patients annually for men and 9.5 for women.[1] The several known risk factors that increase the risk of developing venous thromboembolism are obesity (body mass index (BMI) > 30 kg/m^2), elevated homocysteine, hospitalisation, surgery, immobility, cancer and genetic factors.[2]

Accordingly, different classes of anticoagulants have been developed including: unfractionated heparin, low-molecular-weight heparin (LMWH), factor Xa inhibitors, coumarins and new/novel oral anticoagulants (NOACs). Despite their pharmacokinetic differences, inadvertent haemorrhage remains a potential complication for all anticoagulants. In order to prevent profound haemorrhagic adverse outcomes, individualised patient monitoring is highly recommended.

At present, the most commonly used anticoagulants are the LMWHs. They include: dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, bemiparin and tinzaparin. These anticoagulants all contain an active pentasaccharide sequence that binds to antithrombin. The continuous anticoagulant effect is achieved upon binding this heparin, activating antithrombin, dissociating and subsequently binding to additional antithrombin. This binding produces a conformational change, accelerating antithrombin binding and inactivation of coagulation factors XIIa, IXa, XIa, Xa and thrombin.[3]

LMWHs are administered subcutaneously in doses mostly adjusted to the patient's weight, usually given once daily. Monitoring of LMWHs can be achieved through measuring anti-Xa levels four hours after administration. Routine monitoring is advisable in patients with renal impairment (glomerular filtration rate < 30 ml/min/1.73 m^2), obesity (BMI > 30 kg/m^2) and elderly patients (over 75 years). In the first patient group, LMWH levels can accumulate because of impaired renal clearance. Measuring the anti-Xa level removes this uncertainty and allows dosing to be individually tailored, hereby allowing clinicians to minimise the risk of haemorrhagic complications.

However, it is worth noting that anti-Xa tests differ per specific LMWH. LMWHs with longer saccharide fragments (tinzaparin) tend to inhibit thrombin more profoundly compared with LMWHs with shorter fragments (enoxaparin). These shorter fragment LMWHs target the inhibition of factor Xa more specifically. These differences can be expressed using a factor Xa/FIIa ratio.

As anti-Xa activity assays are considered the 'gold standard' for determining the plasma concentration of LMWH, they do not always correlate well with the in vivo drug effect. Instead, anti-Xa levels can be seen to reflect the pharmacokinetics rather than pharmacodynamics of the relevant LMWH. In a recent study,[4] Thomas et al. suggest that combining anti-Xa levels with an aPTT level can provide essential dosing information in patients at increased risk of anticoagulant-induced haemorrhage, such as in renal impairment.

Nonetheless, in this issue Verhave et al. [5] have demonstrated that in a prophylactic use setting the monitoring of anti-Xa levels alone is sufficient to accurately adjust an individual's LMWH dose. They studied a small group of patients who were treated with LMWHs for prophylactic use in nocturnal haemodialysis. Their dosing algorithm provides a suitable guideline for future monitoring studies. As differences exist between anti-Xa levels for different LMWHs, more studies are needed to determine the type and frequency of anti-Xa monitoring.

Finally, the antineoplastic effect of LMWHs is an area of research that has received considerable attention. A recent

trial reported that LMWHs (i.e. nadroparin) used in cancer patients increased median survival, which showed a larger effect if life expectancy was greater than six months.[6] Mechanistically, a lot of theories have been proposed but more research is needed. This potentially significant discovery could radically alter our perception of the role of anticoagulants.

In conclusion, LMWHs must be considered an essential pharmacological tool to prevent thrombosis. They remain relatively simple to use, requiring once or twice daily administration. However, in certain patient groups their effect can be unpredictable. Therefore, close monitoring with anti-Xa levels or anti-Xa levels and aPTT in combination can provide invaluable information. Finally, the application of anticoagulants solely for thrombosis prevention arguably underestimates their potential.

REFERENCES

1. van der Linden MW, Wester GP, de Bakker DH, Schellevis FG. NHG Standaard Diepe veneuze trombose en longembolie - Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht/ Bilthoven: NIVEL/RIVM 2004.
2. Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol. 2007;44:62-9.
3. Alquqaizani M, Buckley L, Adams C, Fanakos J. Anticoagulants: A review of the pharmacology, dosing and complications. Curr Emerg Hosp Med Rep. 2013;1:83-97.
4. Thomas O, Lybeck E, Tynngard N, et al. Monitoring low molecular weight heparins at therapeutic levels: dose-responses of, and correlations and difference between aPTT, anti-factor Xa, thrombin generation assays. PLoS ONE. 2015;10.
5. Verhave G, Weijmer MC, van Jaarsveld BC. Anticoagulants with dalteparin and nadroparin in nocturnal haemodialysis. Neth J Med. 2015;73:270-5.
6. Klerk CP, Smorenburg SM, Otten HM, et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin Oncol. 2005;23:2130-5.