**Introduction**

There is agreement in the literature regarding the pharmacological inequivalence of LMWHs and there is evidence that differences in pharmacological profiles affect clinical outcomes. Unfractionated heparin (UFH) produces its anticoagulation effects by complexing with antithrombin III (AT III) to inactivate both factor IIa (thrombin) and factor Xa. Inhibition of factor IIa requires a polysaccharide chain of at least 18 polysaccharides, while inactivation of factor Xa does not depend completely on the length of the heparin molecule. The shorter saccharide chains of LMWHs allow for inhibition of activated factor Xa but are not long enough to complex with thrombin and inactivate it as fully as UFH [1]. This preferential effect of LMWHs on factor Xa over thrombin reduces the bleeding potential while prolonging the anticoagulant effect.

LMWHs are a heterogeneous mix of polysaccharide chains of different lengths and weights prepared from UFH by chemical or enzymatic depolymerisation. Bemiparin, a novel second generation LMWH, is produced by a unique selective fractionation process in which UFH is treated with quaternary ammonium to produce a heparin salt [2]. This depolymerisation process protects the key groups of the UFH molecule making it possible to isolate and characterise fragments with a high affinity for anti-thrombin. The first generation LMWHs contained 25–50% of fragments with 18 or more saccharides (molecular weight >6000) while newer agents contain a much lower percentage of long chains (molecular weight >6000 daltons) thus maintaining therapeutic benefit while reducing the risk of bleeding. Bemiparin has an average molecular weight of 3,600 daltons with <15% of ‘critical length’ chains (molecular weight >6000 daltons) [2].

**Pharmacological activity of low molecular weight heparins**

**Anti-Xa/anti-IIa ratio**

The distribution of the LMW fragments has a direct influence on the ratio of their anti-Xa:anti-IIa activities. Experimental studies have shown that bemiparin has an anti-Xa activity of between 80 and 120 IU/mg and its anti-IIa activity ranges from 5–20 IU/mg with a resulting anti-Xa:anti-IIa ratio of 8:1. When compared with other LMWHs and UFH, bemiparin has the highest anti-Xa:anti-IIa ratio (Table 1) [3]. The unique molecular structure and improved activity ratio mean that bemiparin has good therapeutic activity with a low risk of bleeding.

**Release of tissue factor pathway inhibitor**

LMWHs exert an anti-Xa effect through antithrombin III and tissue factor pathway inhibitor (TFPI) displaced from endothelium and lipoproteins. TFPI is a natural coagulation inhibitor synthesised by the endothelium and monocytes and endogenous deposits on the cell wall, which release TFPI following exposure to heparin. In a recent study the localisation, gene expression and activity of TFPI was investigated in...
endothelial cells grown in static conditions or under shear stress [4]. Dalteparin, bemiparin and UFH induced increased release, cellular redistribution and enhanced activity of TFPI, while only bemiparin enhanced TFPI mRNA in endothelial cells under arterial flow. The authors concluded that bemiparin might be superior to conventional heparins in maintaining anticoagulant properties of the endothelium.

**Pharmacokinetics of low molecular weight heparins**

In a three-way crossover study in 12 healthy volunteers, who received subcutaneous bemiparin (30 and 60 mg), the maximal anti-Xa effect was reached 2–4 hours after administration and was not measurable at 12–18 hours [5]. The bioavailability and elimination half-life of bemiparin (96% and 5.3 hours, respectively) are the highest among the LMWHs (Table 1). Similarly, in an open-label, crossover, phase I study, following injection of three subcutaneous doses of bemiparin (7500, 10000 and 12500 anti-Xa IU) the anti-Xa effect peaked between 3–6 hours and showed a dose-dependent response [6]. The absorption and elimination were first-order processes and the long half-life (>5 hours) was constant with increasing doses. At 7500 IU, the anti-Xa effect lasted at least 18–20 hours. Bemiparin was well tolerated and no clinically relevant prolongation of aPTT, prothrombin and thrombin clotting tests were observed. The anti-Xa activity followed a linear dose-response pattern and neither total nor free TFPI was directly proportional to the dose [7]. At therapeutic subcutaneous doses, bemiparin exerted an anti-Xa effect through TFPI during the first 2 hours, through both ATIII and TFPI during the following 8 hours and through ATIII alone during the last 8 hours.

**Conclusion**

Bemiparin belongs to a new second generation LMWH due to its improved pharmacological profile.

**References**