Bemiparin
Pharmacological Profile
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Abstract
Bemiparin is a low molecular weight heparin (LMWH) that has been available in Europe for 10 years and is indicated for thromboprophylaxis and the treatment of deep vein thrombosis. Bemiparin is termed a ‘second-generation’ LMWH, because at 3.6 kDa, it has a lower mean molecular weight than other LMWH and a narrow distribution of saccharide chain lengths, with most being less than 6 kDa. As a result of its low molecular weight, it has low anti-factor IIa (thrombin) activity and an anti-Xa : anti-IIa activity ratio of 8 : 1 compared with a ratio of 1 : 1 for unfractionated heparin. The anti-Xa activity of bemiparin is only partly neutralized by protamine sulphate. In addition to anti-Xa activity, bemiparin increased the release and activity of tissue factor pathway inhibitor (TFPI) from endothelial cells under both static conditions and arterial sheer stress. Bemiparin is rapidly absorbed after subcutaneous administration, attaining maximal plasma anti-Xa activity within 2–6 h. The bioavailability of bemiparin was estimated at 96% and the apparent volume of distribution was 5.1 L. Plasma anti-Xa activity was maintained for up to 12 h with single bemiparin doses of 2500 IU anti-Xa or less and for up to 20–24 h with single doses of 7500–12 500 IU. The area under the effect–time curve for bemiparin increased dose-dependently and was greater than those for slightly higher doses of enoxaparin and tinzaparin. Bemiparin has the longest half-life of all LMWH at 5.3 h compared with 0.5–1.0 h for unfractionated heparin. Elimination is linear, with a mean residence time of over 7 h and total clearance of 0.9 L/h. The peak activity for the TFPI effect was earlier than the anti-Xa effect, at 1–2 h, and lasted for 6–12 h. Bemiparin thus has good antithrombotic activity and a better pharmacological profile than unfractionated heparin.

1. Introduction
Bemiparin (bemiparin sodium) is a low molecular weight heparin (LMWH) produced by alkaline depolymerisation (β-elimination) of medical-grade unfractionated heparin (UFH) sodium derived from porcine intestinal mucosa.[1]

Bemiparin was first marketed in Spain in 1998 and is now widely available in the EU and many other countries worldwide (33 countries in total).[2] It is not currently available in the USA.

In the UK, bemiparin is indicated (at dosages of 2500 or 3500 IU anti-Xa activity/mL) for the prevention of thromboembolic disease in patients undergoing orthopaedic surgery, and for the prevention of clotting in the extracorporeal circuit during haemodialysis.[1,3] It is also indicated at a usual once-daily dosage of 115 IU anti-Xa...
activity/kg bodyweight for the acute treatment of established deep vein thrombosis, with or without pulmonary embolism. In other markets, it is also indicated for the prevention of thromboembolic disease in patients at moderate or high risk of venous thromboembolism (VTE) undergoing general surgery, for prophylaxis in medical patients at moderate or high VTE risk and for secondary prophylaxis to avoid recurrence of VTE in patients with deep vein thrombosis and transient risk factors. It is a LMWH approved for postoperative administration in surgical thromboprophylaxis. It is not approved for use in acute coronary syndromes (unstable angina, non-Q wave myocardial infarction or ST-segment elevation myocardial infarction).

2. Structure

Bemiparin, like all heparins, consists of a heterogeneous mixture of saccharide chains of varying length. Each chain comprises a repeating sequence of disaccharide units consisting of a uronic acid residue (either D-glucuronic acid or L-iduronic acid) and a D-glycosamine residue. Bemiparin is distinct in having a 4-enopyranosyluronate group at its non-reducing end (figure 1).

Bemiparin has been referred to as a ‘second-generation’ LMWH, because it has a lower mean molecular weight than other LMWH at 3.6 kDa (table I), and a precisely defined, narrow distribution of saccharide chain lengths. Less than 35% of chains are below 2 kDa in molecular weight, 50–75% are between 2 and 6 kDa, and less than 15% have a molecular weight higher than 6 kDa. Therefore, bemiparin is likely to have a high proportion of saccharide chains below the critical molecular weight of 5.4 kDa; chains below this length have a substantially longer biological half-life and have more selective anti-Xa activity than longer chains.

3. Mechanism of Action

The antithrombotic and anticoagulant effects of bemiparin, like all LMWH, result from its ability to inactivate factors Xa and IIa (thrombin) by binding to and activating antithrombin, and from its effects on tissue factor pathway inhibitor (TFPI). Binding to antithrombin requires the presence of a high-affinity pentasaccharide unit in the heparin chain; this is usually present in approximately one-third of heparin molecules.

3.1 Anti-Xa and Anti-IIa Activity

Most saccharide chains of UFH contain more than 18 monosaccharide units (i.e. have a molecular weight >5.4 kDa); this is the minimum size required for heparin to bind directly to and inactivate factor IIa, because this inactivation requires heparin to bind to factor IIa and antithrombin simultaneously. In contrast, the inactivation of factor Xa does not require the formation of such a ternary complex, just binding of the heparin to antithrombin through the high-affinity pentasaccharide, and this is accomplished by both large and small saccharide chains. UFH equally inhibits factors Xa and IIa, and has an anti-Xa:anti-IIa activity ratio of 1.0.

Bemiparin contains few chains of sufficient length to inhibit factor IIa. The anti-Xa activity of bemiparin ranges from 80 to 120 IU/mg, whereas anti-IIa activity ranges from 5 to 20 IU/mg.