Treatment of venous thromboembolism: experience with bemiparin

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Introduction

Until a few years ago unfractionated heparin (UFH) was the standard treatment for venous thromboembolism (VTE). The introduction of LMWHs with their unique properties conferred a number of important advantages including greater activity against factor Xa, predictable anticoagulant response, better bioavailability, longer half-life, reduced binding to plasma proteins and macrophages, reduced effects on platelets and less bleeding. A recent meta-analysis of 16 randomised trials in 2045 patients compared the effects of LMWH and UFH on the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE). There was a reduction in mortality, bleeding and the incidence of thrombocytopenia in patients treated with LMWH.

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Although the use of LMWHs during acute treatment of DVT is now well established, their use in long-term treatment remains to be defined. The objective of the presentation is to discuss a major new trial comparing the efficacy and safety of bemiparin and UFH in both the acute and long-term treatment of DVT (table 1). In this multicentre trial, 324 patients with acute venography-proven DVT, were randomised into three groups to receive UFH, initially a 5000 IU bolus followed by i.v. infusion (APTT 1.5–2.5 times baseline) (Group A), bemiparin 115 IU anti-Xa/kg subcutaneously once daily for 7 days (Group B) or bemiparin 115 IU anti-Xa/kg once daily for 10 days followed by maintenance dose 3500 IU anti-Xa daily until the end of 90 days. The primary efficacy outcome variable included the venographically determined change in thrombus size assessed by Marder score between baseline and day 14 (± 2) and symptomatic recurrence of DVT/PE. The efficacy of long term treatment was assessed by patency of the deep venous system determined by venography or Doppler ultrasound at week 12.

In total, 52% of patients in Group A and 72% in groups B and C showed venographic reductions in thrombus size on Day 14 (per protocol analysis) (Table 2). This 20% difference demonstrated not only non-inferiority of bemiparin ($p=0.00003$) but also superiority ($p=0.004$) compared with UFH. On long-term treatment (Day 84), venographic or Doppler sonographic recanalisation of the affected veins was 75.3, 79.8 and 81.5% in groups A, B and C, respectively (Table 3). Mortality, recurrent VTE events and bleeding were similar in all three groups. UFH and bemiparin were well tolerated with a low incidence of adverse events (Table 4). Overall both bemiparin regimens were more effective than UFH in reducing thrombus size during the acute phase of treatment. Bemiparin also appears to be an effective alternative to warfarin in the long-term treatment of VTE.

The details of the study have already been published in *Thromb Haemost* 2003; 89:674-80.

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Table 1. Trial overview**Design**

- Multicentre, randomised, open, parallel trial conducted in the UK, Spain, Portugal

Patients

- 324 patients with acute DVT proven by venography

Treatment

- Group A: Unfractionated heparin, initial 5000 IU bolus followed by i.v. infusion to APTT 1.5–2.5 times baseline
- Group B: Bemiparin 115 IU anti-Xa/kg subcutaneously once daily for 7 days
- Group C: Bemiparin 115 IU anti-Xa/kg subcutaneously once daily for 10 days followed by maintenance dose 3500 IU anti-Xa once daily until the end of 90 days
- Groups A & B: Vitamin K from day 3 for 12 weeks to achieve an INR of 2–3

Assessment criteria

- Efficacy of acute treatment (Days 1–14)
- Venographic improvement (change in Marder score)
- Clinical events (recurrent DVT, PE, death)
- Efficacy of long-term treatment (Days 10–90)
- Deep vein recanalisation
- Clinical events
- Safety (Days 1–90)

Table 2. Improvement in Marder score at Day 14 of treatment (per protocol analysis)

	UFH	Bemiparin	
Treatment	Group A (n=98)	Group B (n=105)	Group C (n=94)
No pf patients improved (%)	51 (52)	76 (72)	68 (72)

Table 3. Recanalisation of affected veins on Day 84 (per protocol analysis)

	UFH	Bemiparin	
Treatment	Group A (n=85)	Group B (n=89)	Group C (n=81)
Recanalisation (%)	64 (75.3)	71 (79.6)	66 (81.5)
Partial	49 (57.6)	56 (62.9)	44 (54.3)
Complete	15 (17.7)	15 (16.9)	22 (27.2)

Table 4. Adverse events

	UFH	Bemiparin	
Treatment	Group A (n=110)	Group B (n=111)	Group C (n=103)
All cause mortality (%)	2 (1.8)	2 (1.8)	1 (1.0)
Minor haemorrhage (%)	1 (0.9)	0	1 (1.0)
Major haemorrhage (%)	1 (0.9)	0	0
Thrombocytopenia (%)	2 (1.8)	2 (1.8)	3 (2.9)