Review

Low-molecular-weight heparins in the treatment of venous thromboembolism

Walter Ageno and Menno V Huisman*

University of Insubria, Varese, Italy, and *Leiden University Medical Centre, Leiden, The Netherlands

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Abstract

Venous thromboembolism is a common disease that is associated with considerable morbidity if left untreated. Recently, low-molecular-weight heparins (LMWHs) have been evaluated for use in acute treatment of deep venous thrombosis and pulmonary embolism. Randomized studies have shown that LMWHs are as effective as unfractionated heparin in the prevention of recurrent venous thromboembolism, and are as safe with respect to the occurrence of major bleeding. A pooled analysis did not show substantial differences among different LMWH compounds used, but no direct comparison of the different LMWHs is currently available. Finally, in patients with pulmonary embolism, there is a relative lack of large studies of daily practice. It could be argued that large prospective studies, in patients who were treated with LMWHs from the moment of diagnosis, are needed.

Keywords: low-molecular-weight heparins, pulmonary embolism, treatment, venous thrombosis

Introduction

Venous thromboembolism is a relatively common disease, and may result in death. Its average annual incidence has been estimated at 48 per 100 000 for deep venous thrombosis and 23 per 100 000 for pulmonary embolism [1]. The clinical significance of venous thromboembolism is not only because of the risk of death from pulmonary embolism, but also because of the high risk of recurrent events, the occurrence of subsequent morbidity such as the post-thrombotic syndrome, and the consequent economic impact caused by the high rate of hospitalization.

Since the early 1960s, anticoagulant therapy has been proven to be pivotal in the treatment of venous thromboembolism. With the exception of massive pulmonary emboli (occurring in <5% of patients who present with pulmonary embolism, in whom thrombolytic therapy should be considered), treatment of established deep venous thrombosis and pulmonary embolism is essentially identical, and includes the administration of heparin for 5–10 days, and oral anticoagulants for at least 3 months [2].

Until recently, unfractionated heparin was the treatment of choice. It can be administered by continuous intravenous infusion, starting with a bolus of 5000 international units (IU) followed by 30 000–35 000 IU/day, adjusted to achieve an activated partial thromboplastin time (APTT) of 1.5–2.5 times the control. Alternatively, after the intravenous bolus injection, unfractionated heparin can be administered subcutaneously, with twice daily injections of 15 000–20 000 IU, which are aimed at maintaining therapeutic levels of APTT.

APTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin; IU = international units.

Careful laboratory monitoring is necessary in order to maintain therapeutic plasma concentrations of heparin. In fact, inadequate anticoagulation may be responsible for a high number of recurrent venous thromboembolic events [3]. It has been reported [4] that patients who receive intravenous heparin without reaching the therapeutic range within the first 24 h may have a rate of recurrence as much as 15 times higher than that in patients who had heparin levels within the therapeutic range.

Unfractionated heparin has a number of limitations. Its anticoagulant effect is unpredictable and varies considerably among patients, depending on age, sex, body weight, smoking status and renal function. This wide variability is caused by heparin binding to acute-phase reactant proteins, levels of which vary among normal individuals and disease states. Before therapeutic plasma levels are achieved, the binding to plasma proteins and to receptor sites on the endothelium must be saturated. Moreover, unfractionated heparin has further effects on haemostasis, such as inhibition of platelet aggregation and augmentation of vessel wall permeability, which can significantly enhance its potential to cause bleeding complications [5]. Finally, as many as 3% of treated patients will develop heparin-induced thrombocytopenia [6].

Pharmacology and pharmacokinetics of LMWHs

LMWHs are obtained by chemical or enzymatic depolymerization of porcine mucosal heparin preparations [7]. Their reduced molecular weight (and thus their reduced number of saccharide units) as compared with unfractionated heparin leads to potential pharmacological and pharmacokinetic advantages over the parent compound, which result in a greater clinical utility. Their antithrombotic activity is mainly based on inactivation of factor Xa because of a reduced ability to inactivate factor IIa when compared with unfractionated heparin. Moreover, the LMWHs do not bind to the endothelium and have a lower affinity for plasma proteins. This results in a more predictable bioavailability, a substantially longer half-life, a stable dose/response relationship when injected subcutaneously, and potentially a more antithrombotic than haemorrhagic activity in comparison with unfractionated heparin [8]. LMWHs also have minimal interaction with platelets, and a reduced incidence of heparin-induced thrombocytopenia has been observed [6]. Because of their properties, the LMWHs can be administered subcutaneously in weight-adjusted, once or twice daily doses without the need for laboratory monitoring.

Randomized trial data

Deep venous thrombosis

In the early 1990s, two randomized trials assessed the efficacy and safety of the LMWHs in the treatment of deep venous thrombosis. In a multicenter, double-blind clinical trial, Hull *et al* [9•] randomized 219 patients to receive unfractionated heparin administered intravenously with an initial bolus of 5000 IU followed by 30 000 IU or 40 000 IU every 24 h (depending on the presence or absence of risk factors for bleeding), and 213 patients to receive a once daily, weight-adjusted dose of the LMWH tinzaparin (175 IU/kg). A nonsignificant reduction in the incidence of recurrent venous thromboembolism (6.9% in the standard heparin-treated group versus 2.8% in the LMWH-treated group), a significant reduction in the rate of major bleeding (5.0% versus 0.5%) and a significant reduction in the rate of deaths (9.6% versus 4.7%) in favour of the LMWH were observed.

In the same year, Prandoni *et al* [10] randomized 170 patients to a similar regimen of unfractionated heparin (a bolus of 100 IU/kg followed by a continous infusion of 35 000 IU every 24 h, adjusted to achieve a target APTT of 1.5–2.0 times control), or to a twice daily, weight-adjusted, subcutaneous administration of the LMWH nadroparin. The results were similar to those reported by Hull *et al* [9•]: in the LMWH group there was a nonsignificant reduction in the rate of recurrent venous thromboembolism (14% in the standard heparin-treated group versus 7% in the LMWH-treated group), a nonsignificant reduction in major bleeding (3.5% versus 1%) and a nonsignificant reduction in deaths after 6 months of follow up (14% versus 7%).

Many other randomized trials subsequently compared the LMWHs with standard heparin in the initial treatment of acute proximal venous thrombosis, and their results were evaluated in three different meta-analyses [11–13], which concluded that LMWHs have greater efficacy and safety. The most recent meta-analysis, including the most recent studies [14•], found no difference between the unfractionated heparin and LMWH (Table 1). The authors of that report concluded that LMWHs have equal effectiveness to that of unfractionated heparin in the prevention of recurrent episodes of venous thromboembolism, and equal safety with respect to the occurrence of major bleeding. Interestingly, a statistically significant reduction in total mortality in patients treated with LMWHs was also found in this meta-analysis. Also, a pooled analysis from the selected trials showed no substantial differences among the different LMWH products used in the studies, but, as correctly recognized by those authors, no direct comparisons of the different LMWHs are actually available. Finally, it is important to note that in all of the above-mentioned trials patients younger than 18 years, pregnant patients and patients with severe renal failure were excluded, and consequently the results of these studies cannot be extrapolated to these specific patient groups.

The simple, unmonitored dosing system and the practical administration of the LMWHs mean that these agents could facilitate outpatient management of deep venous thrombosis. Two large trials published in 1996 have clearly demonstrated the safety and efficacy of such an approach.

Table 1

A meta-analysis comparing LMWH in the treatment of venous thromboembolism

Adverse event	LMWH	Unfractionated heparin	RR (95% CI)	*P*
Recurrent venous thromboembolism	96/2212 (4.3%)	115/2235 (5.1%)	0.85 (0.65–1.12)	0.20
Major haemorrhage	33/2212 (1.5%)	57/2235 (2.5%)	0.63 (0.37–1.05)	0.08
Total mortality	98/2006 (4.9%)	132/2027 (6.5%)	0.76 (0.59–0.98)	0.03

CI, confidence interval; RR, relative risk. Data from Dolovich *et al* [14•].

Table 2

LMWH in the outpatient treatment of deep venous thrombosis

Adverse event	LMWH	Unfractionated heparin	Risk reduction
Recurrent venous thromboembolism	4.45%	7.02%	37%
Major haemorrhage	1.00%	2.31%	57%
Death	4.55%	7.12%	36%

Pooled analysis of the studies of Koopman *et al* [15•] and Levine *et al* [16•].

In the TASMAN study [15•], conducted in Europe, Australia and New Zealand, 198 patients were randomized to receive an adjusted-dose of intravenous unfractionated heparin in the hospital, and 202 patients to receive a fixed, weight-adjusted subcutaneous dose of the LMWH nadroparin, which was administered at home, if it was considered possible. The rate of events was comparable in the two groups with regard to recurrent venous thromboembolism (8.6 and 6.9%, respectively), major bleeding (2.0 and 0.5%, respectively) and death (8.1 and 6.9%, respectively). Importantly, the duration of hospitalization was reduced by 67% from 8.1 days in the unfractionated heparin group to 2.7 days in the LMWH group. In the LMWH group, 75% of the patients were discharged within 2 days or were not even admitted to the hospital.

The second study was carried out in Canada by Levine *et al* [16•] (Table 2). The design of the trial and the sample size were similar to those of the TASMAN study. There were 253 patients randomized to the intravenous unfractionated heparin group, and 247 patients to the LMWH enoxaparin group. The event rates of recurrent venous thromboembolism and major bleeding did not reach statistical significance and therefore it was concluded that the LMWH enoxaparine was not inferior to unfractionated heparin in the treatment of deep venous thrombosis. As in the previous study, the time spent in the hospital was remarkably reduced, from 6.5 days to 1.1 days, and 120 out of the 247 patients randomized to the LMWH were never admitted to the hospital. This study and the TASMAN study [15•] suggest the feasibility of a significant change in the clinical management of patients presenting with deep venous thrombosis, ie treating them at home with LMWH.

Two recently published reports from Canada [17,18] and one from The Netherlands [19] suggest that more than 80% of patients with proximal deep venous thrombosis can safely be treated from the first day with LMWH at home without the need for hospitalization.

From pharmacokinetic data it has been observed that therapeutic anti-Xa levels could be achieved over 24 h when LMWHs are administered once daily. Once daily dosing is attractive because it may be more acceptable to the patient and involves less nursing time. In one controlled study [20], once daily nadroparin was shown to have equal efficacy and safety as twice daily nadroparin. The primary end-point of a combination of venous thromboembolism and mortality was reported in 13 patients (4.1%) in the group that received daily nadroparin and in 24 patients (7.2%) who received twice daily nadroparin. Thus, an absolute difference of 3.1% (95% confidence interval −6.6% to 0.5%) was observed in favour of the once daily therapy. Major bleeding occurred in four patients both in the once daily group (1.3%) and in the twice daily group (1.2%).

Pulmonary embolism

Because deep venous thrombosis and pulmonary embolism are considered two manifestations of the same disease – venous thromboembolism – the LMWHs have also recently been tested in the setting of patients with haemodynamically stable pulmonary embolism. Three trials were published between 1997 and 2000: one was carried out in a population of patients presenting with venous thromboembolism, including submassive pulmonary embolism [21]; one specifically in patients with submassive pulmonary embolism [22]; and a third was conducted

in patients admitted for deep venous thrombosis who also had objectively documented pulmonary embolism [23].

The COLUMBUS trial [21] was an international, randomized, open-label study that enrolled 1021 patients presenting with acute symptomatic deep venous thrombosis, pulmonary embolism, or both. Patients were randomly assigned to one of two groups. One group receive the LMWH reviparin administered subcutaneously twice daily at fixed, weight-adjusted doses (6300 anti-Xa units if body weight was more than 60 kg, 4200 anti-Xa units if body weight was between 46 and 60 kg, and 3500 units for a body weight between 35 and 45 kg). The other group received unfractionated heparin administered intravenously in a 5000 IU bolus followed by a dose of 1250 IU/h, adjusted to achieve an APTT range between 60 and 85 s. Home treatment was encouraged for patients assigned to reviparin. Only 12 patients were excluded because thrombolytic therapy was planned, and 271 patients with pulmonary embolism were included in the study. The total rate of recurrences in the subgroup with pulmonary embolism was comparable to that of the group of patients with deep venous thrombosis (5.9% versus 4.8%, respectively), and was also similar in the two treatment groups (5.8% in the reviparin group versus 6.0% in the unfractionated heparin group). There were six episodes of fatal pulmonary embolism (2.2%) during the 3 months of follow up, all of which occurred in the subgroup of 271 patients enrolled with pulmonary embolism.

The THÉSÉE study [22] was a randomized, multicenter, open-label trial. A total of 612 patients presenting with symptomatic pulmonary embolism were assigned to receive the LMWH tinzaparin administered subcutaneously at a once daily dose of 175 anti-Xa units/kg body weight, or to receive unfractionated heparin administered intravenously with an initial bolus of 50 IU/kg followed by an initial dose of 500 IU/kg, adjusted to achieve therapeutic levels of the APTT between 2 and 3 times the control value. After 8 days, the occurrence of events included in the primary outcome (recurrent venous thromboembolism, major bleeding or death) was similar in the two treatment groups: 2.9% in the unfractionated heparin group and 3.0% in the tinzaparin group. After 90 days this similarity remained, with a 7.1% and 5.9% incidence in the unfractionated heparin and tinzaparin groups, respectively. There was a 1.0% rate of fatal pulmonary emboli in both groups.

The study by Hull *et al* [23] included a subpopulation of an earlier trial [9•] with objectively documented pulmonary embolism with underlying deep venous thrombosis. Patients were assigned to the LMWH tinzaparin, administered, as in the previous study, subcutaneously in a once daily fixed dose of 175 anti-Xa units/kg of body weight, or to unfractionated heparin administered intravenously with an initial bolus of 5000 IU followed by a continuous infusion of 40 320 IU/24 h (or 29 760 IU/24 h for those patients with risk factors for bleeding), which was adjusted to achieve a therapeutic APTT range between 1.5 and 2.5 times the control value. Of the originally included 432 patients with deep venous thrombosis, 200 had high-probability perfusion lung scan findings and were included in this study. Only 28 (14%) had presented with symptoms of pulmonary embolism. There were no recurrent episodes of venous thromboembolism in the group of patients treated with tinzaparin, and seven new episodes (four pulmonary embolisms) in the unfractionated heparin group (95% confidence interval for the difference 1.9% to 11.7%; $P=0.01$). Death occurred in 6.2% and 8.7% of patients, respectively; only in one patient (in the unfractionated heparin group) was death related to pulmonary embolism.

The LMWHs are currently considered a potentially valid alternative to unfractionated heparin in the treatment of pulmonary embolism in patients whose clinical condition is stable. One might argue that there is a need for more clinical studies, involving large groups of unselected patients, presenting with clinically suspected pulmonary embolism, who were treated with LMWHs from the moment of diagnosis.

Conclusion

LMWHs have replaced unfractionated heparin in the initial treatment of patients with deep venous thrombosis. Numerous well-designed clinical trials have demonstrated that LMWHs are as effective and safe as unfractionated heparin and, because no laboratory control is needed, they are the initial treatment of choice for initiating out-of-hospital anticoagulant treatment in patients with acute deep venous thrombosis. For patients with pulmonary embolism, LMWHs are a potential alternative for unfractionated intravenous heparin. Whether all patients with pulmonary embolism can be treated at home from the first day with LMWHs must be assessed in prospective follow-up studies.

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Authors' affiliations: Department of Internal Medicine, University of Insubria, Varese, Italy (Walter Ageno), and Department of General Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands (Menno V Huisman)

Correspondence: Dr Menno V Huisman, Department of General Internal Medicine, Room B3 Q84, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands.
Tel: +31 71 526 3761; e-mail: m.v.huisman@lumc.nl