Low molecular weight heparins: a valuable tool in the treatment of acute coronary syndromes

L. Wallentin

Department of Cardiology, University Hospital, Uppsala, Sweden

Introduction

Since the recognition that thrombosis overlying a ruptured atherosclerotic plaque is a central component of the pathogenesis of the acute coronary syndromes of unstable angina and non-Q wave infarction, a number of antithrombotic treatment strategies have been investigated in randomized clinical trials. Aspirin has been shown to reduce the occurrence of symptomatic and silent ischaemia, myocardial infarction and death in patients with acute coronary syndromes, and is now recommended therapy. Similar benefits have been demonstrated for heparin, which has a number of pharmacological actions, other than its anticoagulant effect, which offer theoretical advantages in the treatment of acute coronary syndromes. These include anti-inflammatory, angiogenic and analgesic actions. Heparin, however, is far from an ideal anticoagulant for the treatment of acute coronary syndromes. Principal among its drawbacks is the impracticality of maintaining a constant and predictable anticoagulant effect without repeated laboratory monitoring. This has restricted its use to short-term treatment during the acute hospital phase of these syndromes, despite increasing evidence that antithrombotic therapy should be maintained for the time taken for the underlying lesion to resolve; 6 weeks–6 months.

Low molecular weight heparins have been shown to be at least as effective as unfractionated heparin in the prevention and treatment of venous thrombosis, and, more recently, have been shown to be effective in preventing arterial and coronary thrombosis. On account of the high bioavailability and predictable pharmacokinetic profile of low molecular weight heparins in comparison with standard heparin, it is possible to maintain an effective and predictable anticoagulant effect with these agents even when given by once- or twice-daily subcutaneous injection. Thus, low molecular weight heparins have similar benefits to heparin in the treatment of acute coronary syndromes, while offering potential improvements in terms of feasibility for long-term therapy. This potential has been confirmed in the first large-scale trial of a low molecular weight heparin in this indication.

Pathophysiology of acute coronary syndromes

The pathophysiology of acute coronary syndromes (i.e. unstable angina and non-Q wave myocardial infarction) has recently been reviewed. The key events are rupture of an atherosclerotic plaque, platelet activation and fibrin deposition, leading to thrombosis. In this respect, acute coronary syndromes can be considered part of a dynamic spectrum of thrombotic complications of coronary artery disease, sometimes being asymptomatic but at other times causing angina, myocardial infarction or sudden death. Evidence that both platelet activation and thrombin generation are involved in the thrombotic process provides the rationale for the use of aspirin and heparin, respectively, in the treatment of acute coronary syndromes.

Heparin

Naturally occurring heparin is a proteoglycan in which glucosaminoglycan chains are covalently bonded to the serine residues of a core protein. It belongs to a family of heparin-related polysaccharides which differ in their...
Heparin is itself a highly heterogeneous group of compounds that differ in the degree to which the glucosaminoglycan chains are deacylated, sulfated and subjected to glucuronic acid polymerization.\textsuperscript{[6]} Pharmaceutical manufacture of heparin involves its extraction from, primarily, bovine lung and porcine intestine, and the subsequent removal of the protein core and degradation of the glucosaminoglycan chains into fragments of 5–30 kDa (17–100 sugar units).

The best-described pharmacological action of heparin is its anticoagulant effect. Heparin interacts with antithrombin causing conformational changes in the latter which render it markedly more effective in inhibiting the coagulation factors, thrombin, \( \text{Xa} \), and \( \text{IXa} \).\textsuperscript{[7–10]} Inhibition of thrombin is by far the most important effect of heparin and occurs via the formation of a ternary complex of heparin, antithrombin and thrombin.\textsuperscript{[7,11,12]} Inhibition of factors \( \text{Xa} \) and \( \text{IXa} \), by contrast, does not require the formation of ternary complexes.\textsuperscript{[7,12–17]} The longer polysaccharide chains of heparin, those greater than 7–2 kDa (24 sugar units), are also able to inhibit thrombin through an interaction with heparin cofactor II.\textsuperscript{[18]}

In addition to these anticoagulant effects, heparin has a number of actions of theoretical value in the treatment of acute coronary syndromes, and coronary artery disease in general.\textsuperscript{[19,20]} These include a variety of anti-inflammatory effects such as inhibition of neutrophil chemotaxis and reduction of myeloperoxidase, lysosomal protease, and free radical activities.\textsuperscript{[21–24]} Inhibitory effects on T-cell function, histamine-induced inflammation and the complement cascade have also been described.\textsuperscript{[25–27]} Furthermore, heparin has antiproliferative effects on vascular smooth muscle cells, decreases plasma viscosity and promotes angiogenesis.\textsuperscript{[28,29]} This latter effect has been reported to improve the development of coronary collateral circulation and myocardial function after myocardial infarction.

### Clinical trials of heparin in acute coronary syndromes

Heparin has been investigated in the treatment of acute coronary syndromes in a surprisingly small number of properly randomized and controlled clinical trials, most of which have included relatively few patients.\textsuperscript{[31–37]} Its efficacy in reducing the incidence of myocardial events in patients with unstable angina or non-Q wave infarction has been confirmed in two placebo-controlled trials. In the first of these, heparin, 10 000 IU four times daily for 7 days, was shown to reduce the incidence of myocardial infarction by 80% during the trial period in patients with unstable angina or non-Q wave infarction.\textsuperscript{[38]} In a second, larger study, similar reductions (>75%) in the risk of myocardial infarction were demonstrated during 6 days of treatment with a continuous intravenous infusion of heparin.\textsuperscript{[32]} The reduction in myocardial infarction with heparin was similar to that obtained with aspirin, 325 mg daily, or the combination of aspirin and heparin. In an extension to the study, however, in which heparin was directly compared with aspirin, treatment with heparin was found to be more effective than aspirin in reducing the incidence of myocardial infarction (0·8% vs 3·7%, \( P=0.035 \)).\textsuperscript{[39]}

The question of whether heparin or aspirin, or indeed a combination of the two, is more effective in the treatment of acute coronary syndromes was complicated by the larger RISC study.\textsuperscript{[40]} Patients treated with aspirin, 75 mg daily, showed a significantly lower incidence of myocardial infarction or death at 5, 30 and 90 days after randomization than patients who received intermittent intravenous injections of heparin, 7500–10 000 IU four times daily for 5 days. During these 5 days, however, the combination of heparin and aspirin seemed to be more effective than aspirin alone. Several explanations may be given for the apparent ineffectiveness of heparin, which alone was no more effective than placebo, in this study. As heparin was administered intermittently rather than by activated partial thromboplastin time (aPTT)-monitored intravenous infusion, it is possible that there were periods during the 5 days of treatment during which patients were inadequately anticoagulated. In a direct comparison of intermittent and continuous heparin infusion in patients with unstable angina or non-Q wave infarction, intermittent injections were found to be significantly less effective than continuous infusion in reducing the frequency of silent ischaemia and angina.\textsuperscript{[41]}

Nonetheless, given the consistency of the data showing that aspirin is effective in reducing both the short- and long-term risk of myocardial infarction after acute coronary syndromes,\textsuperscript{[39–41]} the important question is not whether heparin is more effective than aspirin, but rather whether heparin and aspirin together are any more effective than aspirin alone. This issue was evaluated in a study in which no differences in the frequency of symptomatic and silent ischaemia were found between patients treated with aspirin alone or the combination of aspirin and a continuous intravenous infusion of heparin for 2 days.\textsuperscript{[42]} However, in a recent study with a similar design, it was demonstrated that both intravenous infusion and high-dose subcutaneous heparin, three times daily, in addition to aspirin, effectively reduced signs and symptoms of ischaemia in hospital patients with refractory symptoms of unstable angina.\textsuperscript{[43]} In another study, in which 5–6 days heparin infusion was followed by warfarin anticoagulation for 3 months, the combination of anticoagulant and aspirin was also associated with a lower incidence of recurrent angina, myocardial infarction or death than aspirin alone after 2 weeks (\( P=0.004 \)) and 3 months of treatment (\( P=0.06 \)).\textsuperscript{[37]}

The results of the clinical trials of heparin serve to highlight the drawbacks of heparin in the treatment of acute coronary syndromes. The key issues might relate to maintenance of the anticoagulant effect, which can only be guaranteed with continuous intravenous infusion, and a longer duration of therapy. In most of the clinical trials of heparin therapy in acute coronary
cytopenia, which might occur in 10–20% of patients. A short duration of heparin therapy not only means that patients do not benefit from exposure to an anticoagulant agent during a period when the underlying lesions are still active, but it may also be associated with reactivation of the thrombotic process at the lesion a few hours after cessation of the heparin infusion. This might be somewhat reduced by simultaneous administration of aspirin, although even with this combination there still seems to be an increased recurrence of ischaemic events after terminating heparin therapy. These experiences support the need for prolonged intense antithrombotic therapy.

Long-term heparin therapy in acute coronary syndromes has been little studied. In a small, controlled cross-over study involving 24 patients with unstable angina, low-dose subcutaneous heparin, 12 500 daily, was associated with decreased anginal activity and levels of fibrinopeptide A. In a larger study involving 728 patients who had previously suffered acute myocardial infarction, the same anticoagulant regimen was associated with a 34% reduction in mortality in comparison with control patients. These two studies suggested that long-term heparin treatment is of value in preventing thrombotic complication of coronary artery disease. However, higher and more frequent doses of subcutaneous heparin are needed for treatment of acute coronary syndromes, as demonstrated by a similar reduction in ischaemic episodes by heparin infusion and high doses of subcutaneous heparin three times daily.

Given the requirements for consistent and relatively high levels of anticoagulation during long-term therapy in the treatment of acute coronary syndromes, heparin would appear not to be an entirely ideal anticoagulant. Continuous intravenous infusion would clearly be impractical for long-term therapy, and alternative administration via the subcutaneous route provides little guarantee of predictable and constant anticoagulation.

Heparin also has some other notable drawbacks for long-term therapy. Heparin-induced thrombocytopenia, which might occur in 10–20% of patients treated with heparin for longer term periods, is thought to be caused by antibodies formed in the presence of heparin that induce platelet activation. This is also a link with osteoporosis and there have been case reports on spinal fracture in patients receiving long-term heparin.

### Low molecular weight heparins

Low molecular weight heparins are produced by enzymatic or chemical depolymerization of standard heparin into polysaccharide fragments with a molecular weight of 4–6.5 kDa (13–22 sugar units). They show marked differences with standard heparin in their pharmacokinetic profile and mode of anticoagulant effect.

Low molecular weight heparins have a higher bioavailability after subcutaneous injection than standard heparin, being close to 100% compared with 30%. They also have a half-life 2–4 times that of standard heparin. These pharmacokinetic differences may be explained by the lower propensity for low molecular weight heparins than standard heparin to bind with plasma proteins, such as histidine-rich glycoprotein, PF4, vitronectin, fibrinogen and von Willebrand factor.

Thus, while standard heparin is eliminated in two phases, a rapid saturable phase corresponding to protein binding and a slower phase corresponding to renal clearance, low molecular weight heparins are eliminated almost entirely by the renal route.

The lower rate of protein binding of low molecular weight heparins in comparison with standard heparin also explains the more predictable anticoagulant response that can be obtained at a given dose of low molecular weight heparins. Overall, this combination of predictable anticoagulant response, high bioavailability and long half-life means that an adequate and persistent anticoagulant effect can be achieved with low molecular weight heparins administered by once or twice daily subcutaneous injections at fixed or weight-adjusted doses. In the clinical setting, low molecular weight heparins administered in this way have been shown to compare favourably with dose-adjusted intravenous heparin in the prevention and treatment of venous thromboembolism.

Unlike heparin, which exerts its anticoagulant effect primarily through potentiation of antithrombin inhibition of thrombin, low molecular weight heparins act mostly by antithrombin-mediated inhibition of factor Xa. However, some thrombin inhibition by low molecular weight heparins is retained and is of importance for the antithrombotic effect. It is dependent on the presence of polysaccharide fragments with molecular weight greater than 5400 kDa (18 sugar units) and varies between different low molecular weight heparins. Another effect that may explain the efficacy of low molecular weight heparins, as well as conventional heparin, is the release of tissue-factor inhibitor.

Experimental models suggest that some low molecular weight heparins are associated with fewer haemorrhagic effects than unfractionated heparin for a given level of venous antithrombotic efficacy. These findings have been confirmed in some, but by no means all, comparative clinical studies in the prevention and treatment of venous thromboembolism.

Studies in models of arterial injury have yielded conflicting data regarding the relative antithrombotic efficacy of low molecular weight heparins and standard heparin. Nonetheless, low molecular weight heparins have been shown to be effective in reducing graft occlusion after femoropopliteal bypass, which
would appear to support the contention that low molecular weight heparins might be effective in preventing arterial thrombosis.

Low molecular weight heparins appear to share many of the other potentially useful pharmacological effects of heparin in the treatment of acute coronary syndromes. Thus, they have been shown to have anti-inflammatory and antiproliferative effects. It has also been claimed that low molecular weight heparins, in conjunction with exercise, reduce myocardial ischaemia and enhance the development of coronary collateral circulation in patients with stable coronary artery disease.

Furthermore, it seems that low molecular weight heparins are associated with a lower risk of the unwanted effects of heparin, most notably thrombocytopenia and osteoporosis. Cases of heparin-induced thrombocytopenia with low molecular weight heparins have been reported, but in larger controlled studies the risk seems considerably less that with conventional heparin. Likewise, a study in patients receiving long-term treatment for recurrent venous thromboembolism suggested that low molecular weight heparin was associated with a lower incidence of spinal fracture than standard heparin.

The first large scale randomized clinical trial demonstrating the benefits of low molecular weight heparin in addition to aspirin in acute coronary syndromes was published recently. In this double-blind, randomized, prospective, placebo-controlled trial 1506 patients with unstable coronary artery disease, i.e. unstable angina or non-Q wave myocardial infarction were included. They were randomized to the low molecular weight heparin dalteparin (Fragmin) 120 IE/kg body weight (max 10 000 IU) subcutaneously twice daily or corresponding placebo during the initial 5-8 days.

Anticoagulant treatment with dalteparin 7500 IU once daily, disease reactivation was evident a few days after lowering the dose in some patients. Furthermore, on termination of treatment after 6 weeks, there was still a trend towards reactivation and reinfarction when the dalteparin dose was lowered, after the acute treatment phase. At long-term follow-up, 4-5 months after cessation of treatment, there were no significant differences in occurrence of death, new myocardial infarction or revascularization. There were very few major bleeding events and the majority of patients complied well with the self-administered injections. Only about 10% of patients stopped the treatment at their own request.

Although the gains with the acute phase twice daily dalteparin therapy were maintained by prolonged treatment with dalteparin 7500 IU once daily, disease reactivation was evident a few days after lowering the dose in some patients. Furthermore, on termination of treatment after 6 weeks, there was still a trend towards an increased frequency of ischaemic events in the dalteparin group in comparison with a placebo group, despite the concurrent use of aspirin. These experiences indicate that unstable lesions that increase the risk of thrombotic occlusions may continue to be active for weeks or months after an initial episode of an acute coronary syndrome. It is therefore suggested that a twice daily dose of low molecular weight heparin should be used even in long-term treatment, and that the treatment period probably should be prolonged for at least 3 months.

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Table 1: Myocardial infarction or death during short term acute phase treatment with heparins in addition to aspirin in unstable coronary syndromes (unstable angina or non-Q-wave myocardial infarction) including at least 200 patients

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Patients</th>
<th>Age (median years)</th>
<th>Duration (days)</th>
<th>Placebo + aspirin</th>
<th>Heparin + aspirin</th>
<th>Trial (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion</td>
<td>484</td>
<td>58</td>
<td>5-6</td>
<td>3-7%</td>
<td>0-8%</td>
<td>Thérioux 1988, 1993</td>
</tr>
<tr>
<td>I.V./6 h</td>
<td>399</td>
<td>50</td>
<td>2-4</td>
<td>3-9%</td>
<td>4-3%</td>
<td>ATACS 1994</td>
</tr>
<tr>
<td>Infusion</td>
<td>214</td>
<td>61</td>
<td>5-6</td>
<td>6-3%</td>
<td>1-4%</td>
<td>Holdright 1994</td>
</tr>
<tr>
<td>L.mw s.c.12 h</td>
<td>285</td>
<td>58</td>
<td>2-4</td>
<td>No difference</td>
<td>1-8%</td>
<td>FRISC 1995</td>
</tr>
</tbody>
</table>

I.V. = intravenous; L.mw s.c. = low molecular weight subcutaneous.
How long-term molecular weight heparins might compare with other therapeutic strategies is open to speculation. Warfarin is well established in the long-term treatment of thromboembolic disorders and has been shown to reduce reinfarction rates by about 30% after acute myocardial infarction[90,91]. In clinical practice, this effect may be offset by haemorrhagic complications and the need for regular monitoring of the anticoagulant effect. The possible benefits of a combination of aspirin and low-dose warfarin, which would be associated with a lower risk of side-effects and would not require laboratory monitoring, is currently being evaluated in large-scale clinical trials.

Thrombolytic therapy has been disappointing in the acute phase of acute coronary syndromes, and its use is presently discouraged except in special circumstances. Direct thrombin inhibitors and GPIIb/IIIa platelet receptor antagonists appear promising and are currently being evaluated in large-scale clinical trials in the acute phase of acute coronary syndromes. So far, they are available only for short-term intravenous use and will probably not solve the problem of reactivation of the disease after termination of an initial infusion.

Summary

Standard heparin, low molecular weight heparin and aspirin are at present the only antithrombotic agents of proven value in the initial treatment of patients with an acute coronary syndrome. The combined use of aspirin and one of the heparins for at least 6 days should be considered for all such patients. With their high bioavailability after subcutaneous injection and prolonged half-life, low molecular weight heparins simplify short-term therapy in the acute phase and enable long-term therapy to be maintained on an outpatient basis without the need for repeated laboratory monitoring of antiocoagulant effects. Such long-term therapy would appear to be beneficial, at least in high-risk patients, in the light of increasing evidence that the underlying lesion in acute coronary syndromes resolves over a period of weeks or months.

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