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CARDIOLOGY Rounds™

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The Role of Low Molecular Weight Heparin in the Management of Ischemic Heart Disease

Platelet Activation and Thrombin Generation in Acute Coronary Syndromes

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There is now extensive evidence implicating partial or complete thrombotic occlusion of the coronary artery in the pathogenesis of unstable angina and acute myocardial infarction.[1] The rupture of an atherosclerotic plaque causes platelet activation and aggregation and elicits the coagulation cascade by tissue factor release.The resultant complex of tissue factor and factor VIIa activates factor Xa,which catalyzes formation of thrombin. In turn, thrombin converts fibrinogen to fibrin, stabilizes the thrombus and further activates platelets and amplifies the coagulation cascade.[2,3]

Aspirin and Standard Heparin Therapy in Acute Coronary Syndromes

Since both platelet activation and thrombin generation are involved in the thrombotic process, there is a rationale for the use of both platelet and coagulation inhibitors in the treatment of acute coronary syndromes.Aspirin effectively reduces short and long term risks of myocardial infarction after an episode of unstable coronary artery disease (unstable angina or non-Q wave myocardial infarction).[4,5,6,7] In the acute phase, intravenous heparin infusion for 5-7 days is at least as effective as aspirin, [6,8,9] but the benefits are short lived because of reactivation of the disease soon after the infusion is stopped.[10] Some studies have shown that a combination of heparin and aspirin is more effective than aspirin alone;[6,7,9,11] however, these benefits appear to be lost after termination of the heparin infusion. This likely occurs in unstable coronary artery disease since there is persistent activation of coagulation for up to several months after the acute event.[12,13] Theoretically, a longer period of more intense antithrombotic treatment may be required in these patients. However, heparin is far from an ideal anticoagulant for the treatment of acute coronary syndromes since it is impractical to maintain a constant intravenous infusion and often difficult to obtain a predictable anticoagulant effect without repeated laboratory monitoring. This has restricted the use of heparin to short term treatment during the acute hospital phase of the syndromes.

Low Molecular Weight vs. Standard Unfractionated Heparin

Low molecular weight heparins have been shown to be at least as effective as unfractionated heparin in the prevention and treatment of venous thrombosis,[14, 15,16] and more recently, have been shown to be effective in preventing arterial and coronary thrombosis.[17] The advantages of low molecular weight heparin (molecular weight 4,000 to 6,500) over standard unfractionated heparin (average molecular weight 12,000-15,000) include a better anticoagulant profile and more favourable binding characteristics.[18] Low molecular weight heparin fragments have relatively more anti factor Xa activity than standard heparin, which could lead to an increased antithrombotic effect. They cause less activation of thrombin, less inhibition of platelets, and less vascular permeability, which could lead to less bleeding. Low molecular weight heparin fragments are also less avidly bound to plasma proteins (e.g., histidine-rich glycoprotein, platelet factor 4, vitronectin, fibrinonectin, and von Willebrand factor), have a higher bioavailability after subcutaneous injection (close to 100% vs. 30% with intra-

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venous unfractionated heparin), and have a half life 2-4 times that of standard heparin. 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 also explains the more predictable anticoagulant response that can be obtained at a given low dose of low molecular weight heparin. 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. Thus, low molecular weight heparin might provide the means for simpler short and long term treatment.[17] Additional advantages of low molecular weight heparins include a lower risk of the unwanted effects of standard unfractionated heparin, most notably thrombocytopenia and osteoporosis. While cases of heparin-induced thrombocytopenia with low molecular weight heparins have been reported, large controlled studies suggest that the risk is considerably less than that seen with conventional heparin.[19] 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.[20]

Low Molecular Weight Heparin and Coronary Collaterals

Low molecular weight heparins appear to share many of the potentially useful pharmacological effects of standard heparin in the treatment of acute coronary syndromes, including anti-inflammatory and anti-proliferative effects.[17] In addition, a pilot study of 23 patients with stable coronary artery disease evaluated the impact of exercise and low molecular weight heparin therapy on indirect measures of collateral function to ischemic myocardium.[21] Patients received either placebo or 10,000 IU of dalteparin sodium by subcutaneous injection once daily for two weeks, and 5,000 IU daily for an additional two weeks. During the first two weeks, patients were exercised to their ischemic threshold three times per day. At baseline and four weeks after treatment, treadmill exercising testing, exercise radionuclide ventriculography and 48 hour ambulatory ST segment monitoring were performed. Five factors reflecting collateral function were evaluated before and after treatment including the rate pressure product and duration of treadmill exercise to the point of ischemia (1 mm of ST segment depression), the number and duration of ischemic episodes on ambulatory monitoring, and a change in the left ventricular ejection fraction with exercise. When these factors were considered together in a multivariate analysis, there was a significant improvement in low molecular weight heparin treated patients compared with placebo treated patients (P=0.014), providing preliminary evidence in a small number of patients that exercise and low molecular weight heparin therapy lessened myocardial ischemia.

Low Molecular Weight Heparins and Restenosis Post-Coronary Angioplasty

Various heparin fractions are effective in preventing smooth muscle cell hyperplasia after experimental arterial injury.[22,23,24] The anti-proliferative effects appear to be independent of molecular size and anticoagulant effect.[24] This potential has been explored in several animal models and in humans in an attempt to prevent restenosis following percutaneous transluminal coronary angioplasty (PTCA). Unfortunately, most trials to date utilizing unfractionated and/or low molecular weight heparins have failed to demonstrate a beneficial effect. This includes recent studies utilizing sustained therapy (28 days[25] or 6 weeks[26]) post-PTCA with low molecular weight heparin.

LMWH and Coronary Artery Stenting

Coronary artery stenting reduces both acute complications of coronary angioplasty and restenosis rates but increases sub-acute thrombosis rates and hemorraghic complications when used with warfarin anticoagulation. Therefore, some initial studies have been undertaken to determine whether low molecular weight heparin may have a role in post stenting treatment. Unfortunately, results have not been favourable to this point with one Phase I study[27] substituting low molecular weight heparin for warfarin in 237 consecutive patients. Despite this therapeutic change, sub-acute occlusion occurred in 10.3% of patients suggesting that both warfarin and low molecular weight heparin were ineffective in preventing thrombus formation at the site of stent implantation.

Based on the hypothesis that sub-acute occlusion was more likely to be initiated by platelet aggregation than by contact activation and blood coagulation factors on foreign material, the role of low molecularweight heparin in addition to aspirin and ticlopidine was evaluated in a prospective registry of 2,900 patients in whom coronary artery stenting was performed without warfarin anticoagulation.[28] All patients received 100 mg per day of aspirin and 250 mg per day of ticlopidine for one month. Low molecular weight heparin treatment was progressively reduced in four consecutive stages from one month treatment to none. The registry results suggested that post stenting treatment by ticlopidine and aspirin was an effective alternative to warfarin anticoagulation, achieving low rates of sub-acute closure and bleeding complications. However, low molecular weight heparin treatment did not improve sub-acute reocclusion rates and increase bleeding complications.

Low Molecular Weight Heparin and Left Ventricular Thrombus Formation

Preliminary data showing benefit of low molecular weight heparin (dalteparin) in the prevention of left ventricular thrombus formation after acute anterior myocardial infarction is also available.[29] Seven hundred and seventy-six patients were randomized in a double-blinded fashion to dalteparin 150 U/kg twice daily or placebo. Over 90% of patients had received antecedent streptokinase and aspirin. Blinded therapy was continued for 7-11 days and the incidence of left ventricular thrombus was significantly lower in patients who received low molecular weight heparin (13.8% vs 21.9%, $p<0.05$). There were no significant differences noted between the groups in the incidences of arterial embolism and reinfarction. Major bleeding was more comon in the dalteparin-treated group (2.9% vs 0.3%, $p=0.006$).

Low Molecular Weight Heparin Therapy in Acute Coronary Syndromes

Several trials are underway or have been completed to evaluate low molecular weight heparins in the management of unstable angina and non-Q wave myocardial infarction. In a small, single-blind trial in unstable angina, 219 patients were randomized to one of three treatment groups: aspirin (200 mg daily), aspirin plus regular heparin (400 IU/kg) intravenously, or aspirin plus the low molecular weight heparin nadroparin calcium (214 UIC/kg anti-Xa twice daily) subcutaneously. Recurrent angina and silent myocardial ischemia (detected by Holter monitoring) was significantly less frequent in the low molecular weight heparin as compared to either the aspirin alone or aspirin plus standard intravenous heparin groups. Non-fatal myocardial infarction and urgent revascularization was significantly more common in the aspirin alone treated group. There were no deaths in the study during the in-hospital phase and both minor and major bleeding was more frequent in the standard intravenous heparin treated group. The authors concluded that treatment with aspirin plus a high dose of low molecular weight heparin during the acute phase of unstable angina was significantly better than treatment with aspirin alone or aspirin plus standard heparin.[30]

FRISC study

The first large scale randomized clinical trial demonstrating the benefits of low molecular weight heparin in addition to aspirin in acute coronary syndromes was recently published.[31] The Fragmin during Instability in Coronary Artery Disease (FRISC) study was a double-blind, randomized, prospective, placebo-controlled trial of 1,506 patients with unstable angina or non-Q wave myocardial infarction. Patients were randomized to the low molecular weight heparin dalteparin (Fragmin 120 IU/kg body weight, maximum 10,000 IU) subcutaneously twice daily or corresponding placebo during the initial 5-8 days. Subsequently, anticoagulant treatment with dalteparin 7,500 IU once daily or corresponding placebo was continued for 35-45 days. All patients took aspirin and conventional anti anginal drugs, and, if needed, received intravenous nitroglycerin infusions during the acute phase.

During the first six days, the rate of death and new myocardial infarction was significantly lower in the dalteparin group than in the placebo group (1.8% vs 4.8%; risk ratio 0.37 [95% confidence intervals (CI): 0.20, 0.68]). Furthermore, the need for intravenous heparin (3.8% vs 7.7%; 0.49 [95% CI: 0.32, 0.75]) and the need for revascularization (0.4% vs 1.2%; 0.33 [95% CI: 0.10, 1.10]) was significantly reduced. The composite endpoint of death, myocardial infarction, need for revascularization, and need for intravenous heparin also showed a significant difference in favour of dalteparin (5.4% vs 10.3%; 0.52 [95% CI: 0.37-0.75]).

During the 35-40 day long term treatment, the reductions in death and new myocardial infarction, and the need for revascularization or heparin infusion remained lower in the delteparin-treated group combined: 20.5% vs 25.7%; 0.79 [95% CI: 0.66, 0.95]. However, at long term follow-up (4-5 months) after cessation of treatment, there were no longer significant differences in the occurrence of death, new myocardial infarction, or revascularization. By this time, about a third of the patients had undergone revascularization, and more than half of these procedures had been carried out because of signs of ischemia.

During the acute phase, there were very few major bleeding episodes with no differences between the placebo and dalteparin treated groups (0.5% vs 0.8%). One placebo treated patient had a fatal cerebral bleeding episode after thrombolysis. Minor bleeding (mainly subcutaneously hematoma at injection sites) was more common in the dalteparin than the placebo group (8.2% vs 0.3% in the acute phase and 6.6% vs 3.3% in the long term phase). There were no differences in mean hemoglobin or platelet count between the groups. Anemia, thrombocytopenia, and other side effects were rare in both groups. Compliance with the outpatient injection treatment was excellent with only 11% of patients in the dalteparin group and 8% in the placebo group terminating the injections at their request after 40-50 days of scheduled therapy. The number of withdrawals from treatment was similar in both groups, although there were more because of cardiac complications in the placebo group and more for other reasons (e.g. subcutaneous hematoma and other minor bleeding episode) in the dalteparin treated group.

The FRISC investigators concluded the treatment with dalteparin in addition to aspirin should be considered for at least six days in all patients with unstable angina or non-Q wave myocardial infarction to reduce the risk of new cardiac

events. The main limitation of this European based study relates to the comparison of dalteparin vs. placebo in the setting of aspirin since North American practice much more frequently involves the combination of unfractionated heparin and aspirin in most patients with unstable coronary syndromes. Thus, it can be argued that the true advantage of a low molecular weight heparin over standard intravenous heparin was not established in the study since low molecular weight heparin was compared to a placebo, and there is evidence to support the use of heparin and aspirin rather than either agent alone in unstable angina.[6,7,9,11] Fortunately, two additional studies have been recently completed with the preliminary Fragmin In Unstable Coronary Heart Disease Study (FRIC) results presented by Dr. Graham Turpie from McMaster University (Hamilton, Ontario) at the previous two annual Canadian Cardiovascular Society meetings.[32,33]

FRIC study

The FRIC study compared dalteparin 120 IU/kg subcutaneously twice daily with intravenous heparin in the initial treatment of patients with unstable coronary disease followed by a long term double-blind comparison of dalteparin 7,500 IU/per day subcutaneously with placebo for 40 days. The primary objective of the study was to determine the efficacy and safety of dalteparin in the reduction of death, myocardial infarction, and recurrence of angina between days 6 and 45. A secondary objective was to compare fixed dose subcutaneous dalteparin with adjusted dose intravenous heparin in hospital. Dalteparin was as effective as intravenous heparin in reducing the risk of death, myocardial infarction, in recurrent angina in the acute phase (13.0% vs 12.5%, p=0.99).[32]

During the prolonged treatment phase, (days 6-45) there was no difference in the composite primary endpoint (12.3% in 519 placebo treated patients vs. 12.7% in 512 dalteparin treated patients). Major bleeding rates were similar (dalteparin 0.5% vs placebo 0.4%). The FRIC investigators concluded that the data suggested that low molecular weight heparin was at least as effective in reducing the risk of ischemic outcomes in the acute phase but there was no benefit of adding low molecular weight heparin once daily to aspirin in the long term treatment of unstable coronary disease.[33]

Additional information regarding the role of low molecular weight heparin as compared to unfractionated heparin in unstable angina non-Q wave infarction in the acute phase will be available from the recently completed ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) and TIMI 11B trials.

ESSENCE study

The ESSENCE study was a double-blind, randomized, parallel group, multicentre study comparing subcutaneous enoxaparin (1 mg/kg twice daily) and intravenous dose adjusted unfractionated heparin (dose) in 3,144 patients in Canada, the United States, Europe, and South America. All patients received aspirin and maximal anti ischemic therapy (nitrates and/or beta- and/or calcium channel blocker) as per local practice. The primary endpoint was 14 day recurrent ischemia, myocardial infarction, or death; a comparison will also be made at 48 hours and 30 days. The study was completed in May, 1996, and the results will be presented at the American Heart Association Meeting in November, 1996.

TIMI 11B trial

The TIMI 11B trial will also evaluate the use of enoxaparin vs. unfractionated heparin in the setting of unstable coronary syndromes. In contrast to the ESSENCE study, TIMI 11B will involve an initial intravenous bolus of enoxaparin prior to subcutaneous twice daily weight adjusted doses during the hospital phase and a second comparison of subcutaneous enoxaparin twice daily after discharge for approximately 5 weeks. The composite primary endpoint to evaluate efficacy will be death, non-fatal infarction, and clinical need for revascularization. Recruitment in the TIMI 11B study is ongoing with the final results of the study not anticipated until late 1997 or early 1998.

The potential advantage of enoxaparin (used in ESSENCE and TIMI 11B) as compared to dalteparin (used in FRISC and FRIC) is a greater anti factor Xa to anti factor IIa activity (3:1 vs 2:1), suggesting greater antithrombotic action.

Conclusions

The low molecular weight heparins offer a significant advance in antithrombotic therapy. In each indication in which they have been tested, they have shown equivalence or superiority to standard heparin and appear to be safer. In addition, low molecular weight heparins have far greater clinical utility since they can be administered by subcutaneous injection without frequent monitoring. This advantage will likely simplify short term treatment in the acute phase and may enable long term therapy to be maintained on a outpatient basis if indeed further trials are able to confirm a benefit of prolonged antithrombotic therapy in addition to the use of aspirin following an acute coronary syndrome.

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Abstracts of Interest

Dose Ranging Trial of Enoxaparin for Unstable Angina: Results of TIMI 11 A

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The low molecular weight heparin, enoxaparin(ENOX), is a potent anticoagulant with high bioavailability when given subcutaneously(sc), achieves a predictable antithrombotic effect, and does not require aPTT monitoring. TIMI 11A was a trial of two uninterrupted ENOX regimens given for 14 days to 629 patients(pts) with unstable angina(UA)/non Q-MI(NQMI). While hospitalized(acute phase), the initial cohort(N=320) received ENOX 1.25 mg/kg sc Q12h and the second cohort(N=309) received ENOX 1mg/kg sc Q12h. Post discharge, pts in both dose groups received ENOX 60 mg(wgt ≥ 65 kg) or 40 mg(wgt < 65 kg) sc Q 12h for up to 14 days. THUS: ENOX 1.0 mg/kg sc Q 12h appears to be the maximally tolerated acute phase dose in that it is associated with a rate of major hemorrhage similar to that seen in TIMI 3 B with heparin(3.2%). Prolonged self-treatment with ENOX (40-60mg Q12h) after discharge was feasible and safe. A phase 3 trial, TIMI 11B, is underway to determine the efficacy and safety of an uninterrupted ENOX regimen(acute + chronic phase) for the long-term management of UA/NQMI.

Variable		ENOX 1.25 mg/kg	ENOX 1.0 mg/kg	P
Major Hemorrhage (total)		23(7.2%)	8(2.6%)	0.009
Timing:	In hospital	20(6.3%)	4(1.3%)	0.001
	Post discharge	3(0.9%)	4(1.3%)	NS
Type:	Instrumented	18(5.6%)	6(1.9%)	0.03
	Spontaneous	6(1.9%)	2(0.6%)	NS
Death/MI/Recurrent Ischemia		21(6.6%)	20(6.5%)	NS

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Primary End Point Analysis From the ESSENCE Trial: Enoxaparin vs Unfractionated Heparin in Unstable Angina and Non-Q Wave Infarction.

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Antithrombotic therapy reduces the risk of recurrent ischemic events in patients with unstable angina. The primary aim of the ESSENCE trial was to evaluate the efficacy of enoxaparin (low molecular weight heparin) versus unfractionated heparin, plus aspirin, in patients with rest angina or non-Q wave infarction. Design: A randomized, double-blind, placebo-controlled study of 3180 patients comparing enoxaparin 1mg/kg sc bid, versus unfractionated heparin via continuous iv infusion to maintain the aPTT at 2X control. Patients within 24 hours of the onset of acute myocardial ischemia without ST elevation were eligible and trial therapy was administered for a minimum of 48 hours to a maximum of 8 days. Primary end points analysed were death, MI, or recurrent angina at 14 days. Currently 3019 patients have been randomized in 10 countries. Mean age is 64 years, 33% female, and 46% prior MI. The overall event rates at 14 days are: mortality 1.7% subsequent MI 5.9% and recurrent angina 17%. The composite triple endpoint rate is 23.6% Recruitment should be complete by June, 1996. Full results of the study will be presented.

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