Hotline Editorial

Low molecular weight heparins in acute coronary syndromes

Do we need new pharmacological and invasive treatments in unstable angina?

Although the incidence of myocardial infarction and cardiac death has fallen progressively in many 'first world' countries, the prevalence of admission with suspected infarction or unstable angina continues to rise. This apparent paradox may be explained, at least in part, by aging of the population and heightened awareness of acute coronary disease. Estimates from the U.S.A. suggest that there are approximately 226 cases per 100,000 of population resulting in approximately 3-1 million hospitalization days per annum for suspected unstable angina. Based on diagnostic coding of hospital discharges there are about 120,000 myocardial infarctions per annum in the U.K., about 80,000 diagnosed episodes of unstable angina but another 120,000 hospitalizations for suspected acute coronary disease (Department of Health Statistics 1995–96). Whether the true incidence of unstable angina is increasing is unclear. To devise appropriate treatment strategies we need robust epidemiological data on unstable angina and non-ST segment elevation myocardial infarction and the ability to identify higher and lower risk patients and differentiate them from patients with non-cardiac chest pain.

Valuable data have been obtained from selected study populations (e.g. GUSTO 2B) and prospective registries\(^2\)-\(^3\). The OASIS Registry involved 7977 patients in 95 hospitals across six countries and included patients on the basis of a clinical history of angina plus ECG changes or prior documented coronary disease\(^3\). The event rates are high with a 10% risk of death of myocardial infarction at 6 months, half of this risk occurring in the first 7 days. When combined with refractory angina almost one in four patients suffer one of these events within 6 months, despite current treatment with aspirin, unfractionated heparin and a variable frequency of revascularization. Thus, there is an important clinical need not only for improved identification of patients, but also for improved pharmacological treatment and proven criteria for PTCA/stent implantation.

Current ‘standards of care’ for antiplatelet and antithrombotic treatment

Evidence in support of the role of aspirin over placebo is convincing and comes from the RISC trial, the Veterans Administration trial and the Canadian Multi-Centre Trial, which, combined, demonstrated approximately 50% reduction in cardiac events\(^4\). In consequence, aspirin treatment has been adopted widely and the OASIS Registry demonstrates that it is used in more than 90% of patients\(^3\). Evidence in support of the use of unfractionated heparin is less clearly substantiated. Individual trials have been relatively small in scale and none produced statistically significant evidence of benefit, independently\(^5\). However, a pooled analysis of all of these trials produced highly suggestive evidence of benefit\(^5\) (risk ratio: 0.67 (95% confidence interval, CI), 0.44–1.02) and hence unfractionated heparin has been adopted as part of the ‘standard of care’.

Limitations of unfractionated heparin

Although widely adopted in unstable angina/non-ST segment elevation myocardial infarction, unfractionated heparin has several disadvantages. Most importantly, there is variation in the anticoagulant and antithrombin effect due to the unpredictable levels of binding to plasma proteins, influenced by the acute phase response. Despite multiple adjustments to infusions and repeated partial thromboplastin estimations, heparin control is suboptimal. In the TIMI 9b trial, the partial thromboplastin time was in the therapeutic range only 25% of the time during the first 24 h and only one-third of the time thereafter\(^6\). The remainder of patients were either under or over anticoagulated and even greater variability will occur in clinical practice.

The continuing risk of cardiac events in unstable angina is associated with continuing thrombin and platelet activation. Rebound has been demonstrated after discontinuation of unfractionated heparin, especially in the absence of aspirin\(^7\). Low
molecular weight heparins exhibit longer persistence of activity in the circulation and are more effective against thrombin bound to fibrin or tissue. Anti-thrombin and anti-factor Xa activity of unfractionated heparin are neutralized by platelet factor 4; of significance in unstable angina, as this factor is expressed by activated platelets. The activity of unfractionated heparin against factor Xa is relatively weak compared with low molecular weight heparin (ratio of 1:1 for anti Xa to anti-IIa compared with ratios between 2:1 and 4:1 for low molecular weight heparins). Thus, there are experimental reasons why low molecular weight heparins may be more effective than unfractionated heparin.

The trials of low-molecular weight heparins in unstable angina

The first large scale trial to test low molecular weight heparin against placebo in unstable angina was the FRISC study[8]. In the presence of aspirin, 1506 patients were randomized to dalteparin (twice daily for the first 6 days then once daily in a lower dose for approximately six weeks) and the trial showed a highly significant reduction in the frequency of death or new myocardial infarction at 6 days (1·8% vs 4·8%, risk ratio 0·37, 95% confidence interval 0·20–0·68) with the effects sustained to 42 days but only a non-significant benefit at six months[8]. The trial demonstrated that, in the presence of aspirin, low molecular weight heparin has a significant benefit over placebo and that it is feasible to administer such agents subcutaneously over a prolonged time. The precise duration of administration remains to be determined.

The FRIC trial tested dalteparin against unfractionated heparin in unstable angina with a sample size of 1400 patients and an initially open design (for the first 6 days)[9]. The trial did not produce convincing evidence for a difference between unfractionated heparin and dalteparin but it was rather under-powered, especially in view of the fact that most of the events occurred during the open phase of the trial.

The ESSENCE trial was a double-blind placebo-controlled trial of low molecular weight heparin (enoxaparin) vs unfractionated heparin[10]. The period of administration was between 2 and 8 days (median 2·6 days) which allowed the clinician discretion to lengthen the duration of administration on the basis of clinical and electrocardiographic features. The primary endpoint (death, myocardial infarction or recurrent angina) was reduced from 19·8% to 16·6% at 14 days (odds ratio 0·80 and 95% confidence intervals of 0·67–0·98). The cumulative event rates remained significantly separated to 30 days. The trial was not powered for the combined endpoint of death/myocardial infarction and this double endpoint just failed to reach statistical significance (20·4% risk reduction at 30 days P=0·08)[10].

In this blinded study, there was a significant reduction in revascularization (27% enoxaparin, 32·2% unfractionated heparin, P=0·001) with about a 4 per 100 fewer PTCAs in all countries[10]. There was no increase in the risk of serious bleeding but there was about a 4% excess in minor bleeding, including ecchymoses at the site of subcutaneous injection.

The 1 year follow-up data from ESSENCE were presented at the American College of Cardiology (Atlanta, March 1998). Follow-up was complete in 94·4% for mortality and 92% for all events. The benefits seen at 30 days were sustained (combined endpoint 35·7% heparin, 32·0% enoxaparin, P=0·022, and for death/myocardial infarction 13·5% vs 11·5% respectively, P=0·082).

What issues remain to be resolved?

There is convincing evidence that low molecular weight heparin is more effective than placebo and at least as effective as unfractionated heparin in the treatment of unstable angina and non-ST segment elevation myocardial infarction. The differences between the FRIC trial with dalteparin and the ESSENCE trial with enoxaparin may be due to differences in the drug (anti-Xa to anti-IIa ratio of 2:1 for dalteparin and 3:1 for enoxaparin). However, they may also be due to the fact that the FRIC trial was relatively underpowered and open in the initial phase. Nevertheless, the findings demonstrate that low molecular weight heparins are at least as effective, and based on ESSENCE more effective, than unfractionated heparin.

Would similar benefits be achieved with higher doses of unfractionated heparin? In ESSENCE, patients on unfractionated heparin were in the target range for partial thromboplastin time (55–85 s) about 46%–60% of the time between 12 and 72 h and only 15–20% were sub-therapeutic. Experience from the thrombolytic trials and the IIb/IIIa receptor antagonist studies suggests that increased doses of heparin may increase bleeding risks without measurable improvements in outcome.

For low molecular weight heparins the subcutaneous route of administration, without the need for dose adjustment, has major logistic advantages. However, in the context of intervention, the...
lack of a readily available assay for antithrombin activity results in uncertainty about the amount of adjunctive antithrombin treatment needed.

Additional data are urgently required. Nevertheless, in the trials completed, it was feasible to withhold low molecular weight heparin and switch to unfractionated heparin for scheduled procedures or to supplement with unfractionated heparin for those requiring urgent procedures.

The duration of administration presents a dilemma. The benefits seen in the ESSENCE trial were achieved with a median of 2.6 days of treatment. Whether longer term administration confers additional advantage remains to be resolved and is being tested in the TIMI 11b study. In addition, in TIMI 11b the first dose is given intravenously to overcome any latency in achieving therapeutic antithrombin and anticoagulant effects after subcutaneous administration.

Are the more potent and specific antithrombins (hirudin, hirulog, hirugen) more effective than heparin in acute coronary syndromes? This remains to be resolved. The GUSTO IIb trial demonstrated only a trend in favour of hirudin over heparin (death/myocardial infarction rates 4.5% and 6.0% at 7 days and 8.3% and 9.1% at 30 days), but the optimal dose of these agents may not have been tested and current large scale trials are still underway (OASIS 2).

Will the platelet glycoprotein IIb/IIIa receptor antagonists provide the antithrombotic requirements in unstable angina? Without an antithrombin this is unlikely. The antithrombin and antiplatelet approaches are complementary and potentially synergistic. Exposure of thrombin is a very potent stimulus to platelet activation and in turn activated platelets trigger thrombin activation. The potential for synergism requires to be tested.

Can the results of the trials be extrapolated to the diversity of patients presenting with suspected acute coronary syndromes? Thus far, the trials have deliberately selected relatively higher risk populations. The results are applicable to patients with the clinical syndrome of unstable angina plus electrocardiographic abnormalities or other evidence of coronary disease. As revealed in the FRISC study, troponin may be valuable in identifying high risk patients and separating those with low risk. Whether benefits exceed the risks among low risk patients (no elevation of troponin and no significant ECG abnormality) remains to be determined.

In conclusion, the one year follow-up data from ESSENCE demonstrate that the early benefits are not diminished. If the findings are substantiated by TIMI 11b, then the final chapter may have been written for unfractionated heparin in unstable angina/non-ST elevation myocardial infarction.

K. A. A. FOX
The Royal Infirmary of Edinburgh, Edinburgh, Scotland, U.K.

References