Editorial

Weight watching in cardiology: low molecular weight heparin for acute coronary syndromes

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Heparin is available for clinical use since the 1950’s and has over the last years firmly established its role as the anticoagulant agent of choice in the prevention and treatment of venous thromboembolism as well as in the management of acute coronary syndromes [1]. Heparin anticoagulation, however, has limitations, partly due to the unpredictable bioavailability of the compound and its large inter- and intrindividual biological effect, requiring continuous intravenous infusion, frequent monitoring of anticoagulation and dose adjustments. Furthermore, the present anticoagulant treatment of patients in a number of clinical situations, such as unstable angina, is still associated with unsatisfactory efficacy and safety in a substantial number of patients.

Recently, low molecular weight heparins (LMWH’s), consisting of low molecular weight fragments of depolymerized heparin, have been introduced [2]. In laboratory studies it was shown that LMWH’s have a relatively high anti-factor Xa to anti-factor IIa ratio, which was thought to be beneficial in terms of a better anticoagulant while less hemorrhagic potential. Moreover, LMWH’s were shown to have a near complete bioavailability and a much more predictable pharmacokinetic and pharmacodynamic effect, rendering frequent laboratory monitoring redundant and enabling fixed dosing based on bodyweight via the subcutaneous route.

In clinical studies on the prevention and treatment of venous thromboembolism LMWH’s showed at least equal and in some cases superior efficacy and safety as compared to unfractionated heparin [3,4]. The relatively easy administration of LMWH by once or twice daily subcutaneous administrations has even enabled the home treatment of a large number of patients that previously had to be treated in the hospital with continuous infusion of unfractionated heparin [5].

This success of LMWH in the management of venous thromboembolism has prompted several investigators to study the use of LMWH’s in acute coronary syndromes. Recently, a number of interesting studies on the use of LMWH in patients with unstable angina or non-Q-wave infarction have been reported. In the first of these studies (the FRISC study) the combination LMWH plus aspirin was shown to be superior to aspirin alone (risk ratio for the composite endpoint of death or myocardial infarction: 0.37, 95% confidence interval 0.20–0.68, \( p = 0.001 \) [6]. Bleeding appeared to be more common in the LMWH group than in the control group, although the incidence of major bleeding was not significantly different. Since nowadays most patients with unstable angina are treated with continuous infusion of unfractionated heparin, the comparison between this regimen and LMWH is more appropriate. This comparison was made in three other studies, two of which focused on the treatment of patients during hospitalization for unstable angina (Gurfinkel et al. [7] and the ESSENCE trial [8], respectively) and one on treating patients during hospitalization and the subsequent 30 days (the FRIC trial) [9]. In the largest of these three trials, the ESSENCE study, 3171 patients were included and randomized to either continuous intravenous unfractionated heparin or low molecular weight heparin by subcutaneous injection. Treatment with LMWH resulted in a lower incidence of the composite end-point of death, myocardial infarction or recurrent angina (odds ratio 0.81, 95% confidence interval 0.86–0.96, \( p = 0.02 \)). The incidence of this triple endpoint at 30 days in the LMWH group was 19.8%, indicating that despite the (small) advantage of LMWH still a large number of these patients did not fare well. The incidence of major bleeding (about 7%) was similar in both groups. It should be mentioned, however, that the difference in favour of LMWH was lost after discontinuation of the drug, possibly indicating a rebound phe-

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nomenon. Somewhat less favourable results were obtained in the FRIC trial, that compared LMWH for up to 45 days after hospitalization for unstable angina with intravenous unfractionated heparin in the hospital and no heparin treatment after discharge. There was no difference in the main outcome events (death, myocardial infarction, and recurrence of angina) between the groups and bleeding rates were similar. It was concluded, however, that LMWH, though not superior to unfractionated heparin, was equally effective and might be a suitable alternative to unfractionated heparin, with the mentioned advantages of facilitated dosing and administration.

In conclusion, treatment of patients with unstable angina with LMWH is at least as effective and potentially more effective than treatment with unfractionated heparin. In the mean time, the interest for this treatment modality in other manifestations of acute coronary syndromes has been aroused. For example, small initial studies have focused on the feasibility, efficacy, and safety of LMWH as adjunctive treatment to thrombolytic agents in patients with acute myocardial infarction [10,11]. One other target might be the prevention of restenosis for example after PTCA, in which situation effective inhibition of thrombin has proven to be of importance [12,13]. Besides an effective anticoagulant, LMWH may have a number of other properties, such as modulation of inflammatory responses and cell growth or migration, that might be beneficial in these situations.

One of such properties is highlighted in a report by Libersan et al. in this issue of Cardiovascular Research [14]. The authors of this article elegantly show in a canine model of ischemia and reperfusion that the administration of the LMWH Enoxaparin, with or without concurrent administration of streptokinase, reduces infarct size as compared with the administration of unfractionated heparin. In addition, it was shown that the LMWH, and not unfractionated heparin, reduces myocardial platelet and neutrophil accumulation, processes that are known to be related to attenuation of the benefit of coronary reperfusion on the extent of myocardial infarction. This study is one of a series of studies illustrating that the beneficial effect of LMWH’s, may extend beyond their anticoagulant effect. Indeed, the non-anticoagulant effects of heparin, such as a variety of anti-inflammatory effects and anti-proliferative action on vascular smooth muscle cells [15,16], are shared by LMWH’s. Moreover, recent reports indicate that LMWH’s may even be more effective in some of these effects [17]. Furthermore, usually in contrast to unfractionated heparin, LMWH’s have been claimed to exert some pro-fibrinolytic activity, particularly if used in combination with thrombolytic agents [18,19].

However, apart from all these benefits, one of the most important advantages of LMWH’s over unfractionated heparin may depend on its much more stable pharmacokinetic profile. Indeed, it has been shown that many of the adverse outcome events in patients with acute coronary syndromes are due to inadequate anticoagulation [20]. Anticoagulation with LMWH may offer the benefit of stable and sustained inhibition of coagulation within the therapeutic range. The additional advantage of the relatively simple administration of LMWH may render this therapy more suitable for prolonged treatment, thereby potentially preventing a rebound after abrupt discontinuation of anticoagulant therapy.

In conclusion, although the role of LMWH’s in acute coronary syndromes is not yet fully established and much of the mechanism of its beneficial effect in this situation remains to be elucidated, these new compounds are promising assets for the management of acute coronary syndromes [21].

References

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