Trials and tribulations of thrombin inhibition

Thrombin is a central component in the molecular and cellular response to plaque rupture and therefore pertinent to the entire spectrum of acute coronary syndromes. This serine protease not only promotes the deposition of fibrin strands and further activation of the coagulation cascade, but is also a potent stimulus for platelet activation, induction of adhesion molecules by neutrophils and monocytes, and proliferation of vascular smooth muscle cells. The current regimen of combined antithrombin and antiplatelet therapy with heparin and aspirin, respectively, across the spectrum of acute coronary syndromes is based on the pivotal role played by thrombin as well as activated platelets (to whose activation thrombin also contributes). However, this is not an ideal regimen. Aspirin is a relatively weak antiplatelet agent and the promise of more potent agents is being fulfilled by the platelet glycoprotein IIbIIIa receptor inhibitors. Heparin also leaves much to be desired. It is an indirectly acting drug that catalyzes the inactivation of fluid phase thrombin by antithrombin III, but is unable to inhibit clot-bound thrombin, which therefore remains enzymatically active. In addition to this deficiency, heparin has several other theoretical disadvantages including inhibition by platelet factor IV and marked heterogeneity of its pharmacokinetic and pharmacodynamic properties. Considerable effort has been expended in identifying a safe and effective antithrombin that can inhibit both fluid phase and clot-bound thrombin.

The medicinal leech, hirudo medicinalis, is the source of hirudin, a 65 amino acid compound that binds directly in a 1:1 fashion via its carboxy terminus to the substrate recognition site of thrombin and via its amino terminus to the catalytic centre of thrombin. Nonsulfated forms of hirudin have been produced by recombinant technology by Ciba-Geigy (CGP 39393 also referred to as REVASC® or desirudin) and Hoechst Behringwerke (HBW 023) that are nearly identical in structure and activity to the naturally occurring compound[1]. In experimental studies of coronary thrombosis, hirudin was superior to heparin in facilitating thrombolysis with both tPA and streptokinase[2,3]. Additionally, hirudin was more effective than heparin in preventing thrombus deposition in animal models of deep arterial injury[4].

Pilot studies of patients with stable angina, unstable angina, and acute MI consistently observed that hirudin was more likely than heparin to maintain a stable aPTT in the target range, thus potentially avoiding the periods of inadequate and excessive anticoagulation frequently seen with heparin. Angiographic evidence from the TIMI 5[5] and HIT[6] trials of myocardial infarction patients treated with tPA, indicated that hirudin achieved 90 min infarct-related artery patency rates equivalent to or superior to those seen with heparin. In unstable angina patients with evidence of coronary thrombus, hirudin appeared to be more effective than heparin in improving the angiographic appearance of the coronary lesion[7].

Given the combination of promising experimental and pilot clinical data noted above, phase III trials of hirudin in acute coronary syndromes were initiated to test whether the direct antithrombin hirudin was superior to the indirect antithrombin heparin. However, the TIMI 9A[8], GUSTO 2A[9] and HIT III[10] trials were all terminated prematurely because unacceptably high rates of intracranial haemorrhage occurred in patients at higher risk than those in the pilot studies. Following reduction of the doses of both heparin (bolus 5000 U and infusion of 1000 U h−1) and hirudin (bolus 0.1 mg kg−1 and infusion of 0.1 mg kg−1 h−1) and introduction of additional safety measures (titration of both anti-thrombins to a reduced target aPTT range of 55–85 s), the TIMI 9B and GUSTO 2B trials were undertaken.

The TIMI 9B trial was presented before the American Heart Association Scientific Session in November, 1995[11]. This trial enrolled 3002 patients with myocardial infarction treated with aspirin and either accelerated dose tPA, or streptokinase. The primary endpoint of unsatisfactory outcome (death, recurrent non-fatal myocardial infarction, or development of severe congestive heart failure or cardiogenic shock by 30 days) occurred in 11.9% of the 1491 heparin-treated patients and in 12.9% of the 1511 hirudin-treated patients (OR (hirudin:heparin) 0.88, 0.73–1.09, 0.88–1.36). By 30 days, the sum of death and non-fatal reinfarction was no different between the treatment groups (hirudin 9.7% vs heparin 9.5%, OR 1.02, 0.80–1.31). Subgroup analyses did not reveal
any profile of patients who benefited more from one of the antithrombins. A multivariate logistic regression analysis indicated that previously established risk factors for a poor prognosis (age, systolic blood pressure, heart rate, location of myocardial infarction, history of prior myocardial infarction, gender, weight) were each highly correlated with adverse outcome. After adjustment for baseline variables, there was no statistical evidence that the anti-thrombin to which the patient was randomized or the time to treatment following initiation of thrombolysis correlated with unsatisfactory outcome or the sum of death and reinfarction by 30 days. The rate of major haemorrhage was similar in the heparin (5.3%) and hirudin (4.6%) groups; intracranial haemorrhage occurred in 0-9% of the heparin and 0-4% of the hirudin patients.

A preliminary report of the GUSTO 2B trial, presented at the American College of Cardiology Scientific Sessions in March 1996[12] indicated that among the 3053 patients with ST segment elevation treated with thrombolytics, the primary endpoint of death and non-fatal reinfarction at 30 days occurred in 12.1% of 1526 heparin-treated patients and 10.3% of 1527 hirudin-treated patients (OR 0.84; 0.67-1.05). In the 1076 patients with ST segment elevation at presentation not treated with thrombolytics, the rate was 9.3% in 530 heparin patients and 9.2% in 546 hirudin patients (OR 0.99; 0.65-1.49). Within the subset of patients without ST segment elevation at presentation, death and reinfarction occurred in 9.1% of 4017 heparin patients and 8.3% of 3992 hirudin patients (OR 0.91; 0.78-1.06). Among patients with ST segment elevation, intracranial haemorrhage occurred in 0.5% and 0.4% of those treated with hirudin and heparin, respectively. In patients without ST segment elevation, the rates were 0.2% for hirudin and 0.02% for heparin.

A formal meta-analysis combining the data from TIMI 9B and GUSTO 2B is in the process of being completed. However, preliminary findings in the combined group of 6055 thrombolytic treated patients and the total of 15140 patients with acute coronary syndromes between the two trials suggests no evidence of a mortality reduction by 30 days with hirudin compared to heparin. Slight reductions of borderline significance in the rate of reinfarction were seen in the pooled thrombolytic group and the entire spectrum of acute coronary syndrome patients.

Hirudin was significantly more likely to maintain the aPTT in the target range, in both TIMI 9B and GUSTO 2B. However, given the totality of data available it does not appear that this advantage translates into clear clinical superiority. In doses that do not cause an undue risk of bleeding the two drugs appear therapeutically equivalent in patients with an acute coronary syndrome.

Why might this be the case, what lessons are to be learned, and what are the implications for future clinical investigation? Although hirudin has a greater ability to decrease thrombin activity (inhibition of fluid-phase and clot-bound thrombin) heparin has a greater ability to decrease thrombin generation (inhibition of earlier steps in the coagulation cascade that are not effected by hirudin)[13,14]. The net result appears to be an equivalent decrement in thrombus deposition in the culprit coronary vessel. The studies of direct thrombin inhibition also underscore the uncertainty of conclusions based on safety observations in phase II trials with a relatively small sample size (e.g. infrequent events may not be adequately represented) and the need for caution in extrapolating acute phase angiographic findings to later clinical events. Future approaches to antithrombotic therapy may require a carefully titrated combination of agents capable of inhibiting the coagulation cascade at multiple sites along with a more potent inhibitor of platelet aggregation, such as a glycoprotein IIb/IIIa antagonist. There is no doubt that effective antithrombin and antiplatelet drug combinations can be devised. However, given the unacceptable risks of serious bleeding in TIMI 9A[8], GUSTO 2A[9] and HIT III[10], the challenge for investigators designing future trials will be to identify an effective regimen that also has an acceptable safety profile.

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References


