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Acute ischemic syndromes and new antithrombotic agents

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Plaque rupture and coronary thrombus formation is critical in the pathogenesis of acute ischemic syndromes. Despite successful pharmacologic therapy directed at thrombolysis, antithrombotic treatment remains suboptimal.

ASA and heparin have been proven effective in acute ischemic syndromes. Integral to the occlusion of a coronary artery is the activation, adhesion and aggregation of platelets. Although ASA interferes with this process it is a relatively weak antiplatelet agent and recently more potent antiplatelet agents have been developed[1]. Heparin, the standard antithrombin, acts indirectly with antithrombin III to inactivate free thrombin; it has no affinity for clot bound thrombin and is bound or inactivated by several plasma proteins and platelet factor 4. In addition, heparin requires monitoring, may produce a variable anticoagulant effect and may be associated with thrombocytopenia[2]. Given the mechanism of action of ASA and heparin, drug therapies targeting novel mechanisms of thrombus formation inhibition may prove beneficial.

In the attempt to improve upon the effectiveness of ASA as an antiplatelet drug,attention has been focused upon the glycoprotein IIb/IIIa receptor. The gp IIb/IIIa receptor is integral in the final common pathway of platelet aggregation which involves binding of fibrinogen to the gp IIb/IIIa receptor. Compounds that have been studied as inhibitors of gp IIb/IIIa receptor include a monoclonal antibody c7E3, Integrelin a cyclic heptapeptide, and Lamifiban and Tirofiban which are peptide-like molecules derived from the structure of Trigramin which is isolated from the venom of the viper *Trimeresurus gramineus*[1].

Recent trials with gp IIb/IIIa receptor inhibitors are summarized in Table 1. The EPIC[3] trial, CAPTURE[4] and EPILOG[7] used the monoclonal antibody c7E3 in the setting of either unstable patients for coronary intervention (EPIC and CAPTURE) or elective angioplasty (EPILOG). CAPTURE and EPILOG were terminated prematurely due to demonstrated benefit in the treatment groups. The EPIC trial also studied the effect of c7E3 and demonstrated a benefit out to 6 months of follow up in a group of "high risk" interventional patients. The IMPACT II[4] study was a continuation of the IMPACT[9] trial, a pilot study demonstrating the beneficial effect of integrelin in patients for elective angioplasty.

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Despite a much larger sample size, IMPACT II failed to demonstrate a statistically significant effect at the 30 day endpoint. The MK-383 (tirofiban) study[6] was carried out in patients with unstable angina/NQWMI. In this small sample size the drug appeared to be effective in decreasing the chosen endpoint of refractory angina. A common finding in these trials was the tendency to increase bleeding risk especially in those patients who were also receiving heparin. However, inhibition of the gp IIb/IIIa receptor appears to be a promising new therapy in the treatment of acute ischemic syndromes. Large planned trials of lamifiban (PARAGON trial) should provide further support in this regard.

Thrombin is the key regulator of the thrombotic process which is central in the pathogenesis of myocardial infarction. It is generated from prothrombin by the prothrombinase complex-factors Xa, Va, calcium and phospholipids, with factor Xa cleaving the prothrombin molecule forming α-thrombin, a combination of A and B chains. Thrombin catalyzes the transformation of fibrinogen to fibrin and is one of the most potent agonists for platelet aggregation. Counterregulatory features of thrombin activation include the activation of

TABLE I

Name	# of pts	Intervention	Patient characteristics	Follow up	Endpoint	Results (active vs placebo)
EPIC[3]	2099	c7E3 bolus± infusion	"high risk" coronary intervention	6 months	Composite: death/MI/ CABG/PTCA	8.3% vs 12.8% p= 0.008
IMPACT II[4]	4010	Integrelin bolus + 2 doses of infusion	Elective PTCA	30 days	Death/MI urgent intervention	9.5% vs 11.4% NS
CAPTURE[5]	1400 (enrollment concluded prematurely)	c7E3 bolus + infusion	Unstable angina (prior to PTCA x 24 hr)	30 days	Death/MI urgent intervention	10.8% vs 16.4% p=0.0064
MK-383[6] (tirofiban)	102	tirofiban bolus & infusion, dose ranging OR heparin	Unstable angina & NQWMI	48 hours	Refractory angina	1% vs 13%
EPILOG[7]	1500 (enrollment concluded prematurely)	c7E3 bolus+ infusion with low or standard dose heparin	Elective PTCA	?	Death/MI	2.6% & 3.6% vs 8.1%
Ro-44-9883[8] (lamifiban)	365	lamifiban bolus & infusion, dose ranging	Unstable angina	?	Death/MI & recurrent angina	12.1% (5 µg dose) vs 30.2%

protein C and S through thrombomodulin which inactivate factors Va and VIIIa. The thrombin molecule is thought to have several binding sites: the catalytic binding site,the anion-binding site or substrate recognition site (fibrinogen binding site) and a separate binding site for fibrin distinct from its fibrinogen binding site. Compounds which are direct thrombin inhibitors are able to bind to clot bound thrombin (unlike heparin) without displacing the thrombin molecule from the fibrin surface.

Hirudin, the prototypical antithrombin, was isolated from leech (*Hirudo medicinalis*) saliva in the 1950's[10]. Derivatives based on the structure of hirudin include hirulog, hirugen, PPACK and argatroban. Hirudin and hirulog bind with strong affinity to both the catalytic binding site and the anion-binding exosite[2]. Direct thrombin inhibitors have been tested in pilot studies and have shown benefit in angiographic and clinical outcomes. These agents were to be tested in patients with coronary artery disease in 3 large scale trials: Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO-IIA)[11], TIMI-9A[12] and HIT-III[13].

GUSTO-IIA was intended to enroll 12,000 patients in a trial involving hirudin in acute coronary syndromes including unstable angina, non-Q wave myocardial infarction and ST-segment elevation infarction. The TIMI 9A trial also compared heparin versus hirudin as adjunctive therapy for thrombolysis in myocardial infarction. Patients with acute ST elevation and duration of ischemic discomfort less than 12 hours were enrolled. The trial, r-Hirudin for Improvement of Thrombolysis, HIT-III, planned an enrollment of 1000 patients to be recruited by 93 German centers. Patients with symptoms of acute MI with onset less than 6 hours prior to presentation were to be randomized to receive either weight based heparin or r-hirudin. The dose of hirudin was less than that used in TIMI 9A or GUSTO IIA. All three of these trials with hirudin were prematurely suspended due to bleeding complications.

Increased bleeding rates and more importantly increased hemorrhagic stroke rates were inordinately high in HIT III, GUSTO II and TIMI 9. Prior experience with anticoagulants alone showed that intracranial bleeds (ICB's) occurred with an incidence of approximately 0.4%[14]. Subsequently, in patients treated with fibrinolytic agents and anticoagulants, the observed rate of intracranial bleeds was slightly higher, 0.4% to 0.7%[14]. In GUSTO I[15], ICB's occurred in 0.5% of patients treated with streptokinase and 0.7% of patients treated with tPA in addition to intravenous heparin. In contrast, the 3 to 5 fold increase in ICB rate seen in HIT III, GUSTO IIA and TIMI 9A was unexpected and not predicted from previous pilot and dose ranging studies. This experience highlights the importance of delineating critical risk factors for ICB's, improved monitoring of anticoagulation and optimal duration and dosage of specific anticoagulants. The reduced dosage regime of heparin and hirudin in GUSTO IIB[16] and TIMI 9B[17] was successful in lowering bleeding incidence.

The results of recent trials with direct antithrombins are detailed in Table 2. GUSTO IIB failed to show a clear statistically significant effect in patients with acute ischemic syndromes. Certain subgroups, the ST ↑ cohort, did however, demonstrate benefit in the first 24 hours. TIMI 9B enrolled those patients with ST elevation given thrombolysis. Similarly, in this trial, hirudin did not seem to offer any treatment advantage over heparin. The OASIS study[18] involved patients with unstable angina and non-Q wave infarction. The results available at present indicate a statistically significant benefit in a combined endpoint at 7 days. However, no significant difference was seen in the "hard" endpoint of death and MI. HERO-I[19] enrolled 412 patients in an angiographic trial whose primary endpoint was the effects of another antithrombin, hirulog, versus heparin on TIMI 3 flow at 90 minutes after thrombolytic treatment with streptokinase. The number of patients in this trial was small and overall analysis revealed a trend that was not

TABLE II

name	# of pts	intervention	patient character-istics	Follow up	Endpoint	results (active vs placebo)
GUSTO IIB[16]	12,141	Hirudin bolus & infusion	AMI ST↑ NQWMI unstable angina	30 days	Death/MI	8.9% vs 9.8% NS
TIMI 9B[17]	3,002	Hirudin bolus & infusion	AMI ST↑	30 days	Death/MI CHF/Shock	12.8% vs 11.8% NS
OASIS[18]	600	Hirudin bolus & infusion (2 doses)	Unstable angina & NQWMI	7 days	Death/MI refractory angina	8.7 & 15.4% vs 17.0% p=0.05
HERO-I[19]	412	Hirulog bolus & infusion, (dose ranging)	AMI ST↑	Angiographic	TIMI 3 flow at 90 minutes	50% vs 35% NS

statistically significant but in favor of increased patency at 90 minutes with hirulog. In GUSTO I, the 90 minute TIMI 3 flow rate was 32%[20], while in the HERO I trial, the patients who received the high dose of hirulog achieved a rate of 50%. Given the results of these recently completed and ongoing trials, it is difficult to reach a definite conclusion concerning the clinical role of direct antithrombin agents in acute ischemic syndromes.

The initial experience with direct antithrombins in acute coronary syndromes demonstrated promising results. Extrapolation of these findings to large multicentered trials revealed an inordinately high bleeding rate which appeared to be a dose dependent phenomena and further study with lower doses of these anticoagulants achieved an improved safety profile. However, no clear benefit with respect to reduction in mortality or reinfarction has been demonstrated in patients with acute ischemic syndromes. It is clear that further experience with newer antithrombotic regimes is required to provide data on the complex interplay of angiographic patency, clinical benefit, and bleeding complications. Combination therapy of gp IIb/IIIa inhibitors and direct thrombin inhibitors may be most efficacious but is yet to be explored.

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Upcoming Scientific Meetings

13-17 July 96
66th Congress of the European Atherosclerosis Society
Florence, Italy
(Fondazione Giovanni Lorenzini Medical Science Foundation)
Tel.: 39 2 29006267

21-24 July 96
6th World Congress of the International Society of Cardiothoracic Surgeons (ISCTS) and 9th Annual Meeting of the ISCTS-Japan Chapter
Hiroshima, Japan
(Simul International, Inc.)
Tel.: 81 3 3586 8691

4-7 August 96
44th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand
Brisbane, Australia
(Kevin J Wickman Pty Ltd.)
Tel.: 61 3 859 6899

25-28 August 96
XVIIIth Congress of the European Society of Cardiology
Birmingham, United Kingdom
(European Congress Organization)
Tel.: 33 92 94 76 21

25-29 September 96
The Royal College of Physicians and Surgeons of Canada 65th Annual Meeting
Halifax, Nova Scotia
(Royal College of Physicians and Surgeons of Canada)
Tel.: 613-730-8177

29 October-2 November 96
Canadian Cardiovascular Society 1996 Annual Meeting
Montreal, Quebec
(Canadian Cardiovascular Society)
Tel.: 604-681-5226

Abstracts of Interest

Prothrombotic importance of the Factor V Leiden genotype mutation in acute coronary syndromes.

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The Factor V Leiden genotype has been shown to predispose to intravascular thrombosis. We examined the prothrombotic potential of this mutation in patients admitted with acute coronary syndromes. 194 patients admitted with chest pain to a single coronary care unit were studied and followed for outcome for a median of three years. DNA was isolated, PCR and restriction analysis was performed and cases of heterozygous Factor V Leiden confirmed by direct genomic sequencing. The genotype frequency was the same as the normal population in both patients with myocardial infarction (7/99, 7.1%) and unstable angina (5/72, 6.9%). On follow up however 9/12 (75%) of the patients admitted with acute coronary syndromes with Factor V Leiden ran a complicated course (reinfarction, need for revascularisation or cardiac death) as compared to 86/159 (54%) of patients without the mutation.

Conclusion. Whilst the Factor V Leiden mutation does not appear to predispose to arterial thrombosis, once activation of coagulation has taken place it appears to predispose to thrombotic complications and merits further evaluation.

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Hirudin ("Revasc) vs Heparin after thrombolysis in acute myocardial infarction: preliminary results from the TIMI 9B Study

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In acute myocardial infarction (AMI) up to 55% of patients fail to attain adequate reperfusion despite aspirin and thrombolytic therapy, and re-occlusion can occur in a further 5-10%. While heparin can reduce re-occlusion after tPA, it acts only on circulating thrombin, and requires dose titration. Hirudin, a potent direct anti-thrombin, inhibits clot-bound thrombin and has a more stable therapeutic effect.

In this international, multi-centre, double blind randomised study, 3002 patients, presenting within 12 h of onset of AMI with ST segment elevation, were treated with oral aspirin, either tPA or streptokinase, and then randomised to either i.v. heparin (1496), or hirudin (1506) for 96 hours titrated to a target APTT of 55-85 secs.

Baseline characteristics were similar between the two groups. Mean age of the population was 60 yrs and 74% were males. Mean time to thrombolysis was 3.3 hrs from symptom onset, and study drug was administered at a mean of 42 min after thrombolysis. Hirudin treated patients were more likely to be within the target APTT range at each time point of measurement than those on heparin. Death, non-fatal reinfarction, or cardiogenic shock occurred in 11.8% of patients on heparin, and 12.8% on hirudin (P=NS). Mortality and re-infarction rates were similar in the two study groups (5.0% vs 6.2%, and 4.9% vs 5.4% for heparin and hirudin respectively). Major haemorrhage occurred in 4.9% of patients on heparin, and in 4.4% on hirudin, (P=NS). Intra-cranial bleeding occurred in 0.7%, and 0.4% of heparin and hirudin treated patients respectively. Bleeding rates were lower in this study compared to the TIMI 9A cohort, where higher doses of both heparin and hirudin were used, the hirudin dose was constant, and a higher target APTT range (60-90 s) was employed.

Conclusion. Hirudin produces a more stable anti-coagulant response than heparin, but is as effective as heparin in AMI after thrombolysis and is associated with a similar risk profile in terms of haemorrhage.

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