The Role of Antithrombin Agents and Factor Xa-Inhibitors in Antithrombotic Treatment

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ABSTRACT

Hirudin, the first specific thrombin inhibitor, which was used clinically, stems from medicinal leeches and is produced today by recombinant technology. R-hirudins have been studied in many clinical trials. R-hirudin has been shown to be more effective than low molecular weight heparin in the prevention of deep venous thrombosis after total hip replacement. In acute coronary syndromes hirudin and the chimeric oligoaminoacid peptide bivalirudin have also been effective. In acute coronary syndromes and when administered together with aspirin high doses of hirudin were associated with an increased risk of bleeding. Hirudin and argatroban successfully prevented thrombotic episodes in patients with heparin-induced thrombocytopenia type II. Several new orally active specific thrombin inhibitors are in development. The combined use of subcutaneous and oral administration of ximelagatran in patients with hip or knee replacement has led to promising results. It seems likely that in the future oral thrombin inhibitors may replace vitamin K-antagonists in some indications.

The pentasaccharide fondaparinux is an indirect inhibitor of F Xa. Its anticoagulant and antithrombotic effect depends on the activation of antithrombin. Fondaparinux has shown remarkable antithrombotic efficacy in patients with high risk orthopedic surgery and has been approved in the US and in Europe. Several new low molecular weight specific F Xa-inhibitors are in different stages of development for i.v. and oral use.

Key Words: Hirudin, LMWH, Bivalirudin, Antithrombotic treatment.

Turk J Haematol 2002;19(2):113-120

During the last 20 years low molecular weigth heparin (LMVH)s have replaced unfractionated heparin (UFH) in many indications. UFH has an about equal inhibiting effect on thrombin and the coagulation factor Xa. Heparins are indirect inhibitors of thrombin and F Xa. They as well as the new pentasaccharide (fondaparinux) activate the plasma proteins antithrombin and heparin cofactor II and this mechanism leads to their anticoagulant effects. Improvements in the prophylaxis and treatment of thromboembolic diseases are expected from direct thrombin or F Xa-inhibitors. Specific thrombin inhibitors are independent of the plasma level of antithrombin and of the inactivation of thrombin by heparin cofactor II.

Thrombin plays a central role in regulating thrombotic processes (Table 1). It influences the permeability of platelet membranes and has other actions of diffe-

rent cell systems, including the stimulation of synthesis and release of mediators from vascular endothelium. After the characterization of the first specific thrombin inhibitor hirudin by Fritz Markwardt other thrombin inhibitors have been detected in different haematophagus animals[1]. Today hirudin is produced by recombinant technology and several new low molecular weight thrombin inhibitors have been developed.

The synthetic pentasaccharide fondaparinux is the smallest form of a low molecular weight heparin with a molecular weight of 1764 D and inhibits F Xa via activation of antithrombin.

Hirudin, other thrombin inhibitors and fondaparinux have been studied in large scale clinical trials and several oral thrombin-and F Xa-inhibitors are in different stages of development by different pharmaceutical companies.

PARENTERAL THROMBIN INHIBITORS (Table 2)

Hirudin

Hirudin was originally obtained from the salival glands of the medicinal leech (hirudo medicinalis) and was first isolated and characterized by Markwardt in 1957[2]. Since approximately 20 years it is produced by recombinant technology (R-hirudin). R-hirudins are as active and specific as natural hirudin. Hirudin derived molecules as hirulog have been used in different clinical trials[3,4].

Methods for the monitoring of hirudin and other thrombin inhibitors: Measurement of the thrombin inhibiting effect (anti-F-IIa-activity) in plasma using a chromogenic substrate probably is the most precise method to monitor prophylaxis or treatment with hirudin and other thrombin inhibitors. More simple, practical and especially suited for bedside monitoring is the ecarin clotting time (ECT)[5,6]. The ECT is well correlated with the inhibition of thrombin as measured with chromogenic substrates. Other methods including the activated partial thromboplastin time (aPTT) and the activated clotting time (ACT) can also be used to monitor the effect of thrombin inhibitors. These methods, however, are not specific and are modified by acquired and inborn coagulation defects and in addition they are not well standardized. The thrombin time is over sensitive and therefore less suited for the control of thrombin inhibitors[7].

Hirudin in coronary heart disease: Large clinical trials with R-hirudin in patients with unstable angina, patients with acute myocardial infarctions or acute coronary syndromes and after coronary angioplasty have been published[8-14].

In the two largest studies (GUSTO 2a and TIMI 9a) a relative high initial intravenous bolus of 0.6 mg/kg hirudin was followed by a continuous infusion of 0.2 mg/kg/h[9,12]. All patients received aspirin and many were also treated with thrombolytic agents. Both studies were stopped because of increased intracranial bleedings and in the GUSTO 2a-study increased mortality had been observed in the hirudin arms. In the TIMI 9a-study there were 14% major bleedings in the hirudin group compared to 10% in the heparin group.

Both studies were restardet with a much lower initial intravenous bolus of 0.1 mg/kg followed by an intravenous infusion 0.1 mg/kg/h. Following this change;

Table 1. Plasmatic and cellular effects of thrombin and factor Xa

Thrombin		Factor Xa
Procoagulant action		Procoagulant action
Fibrinogen	Æ fibrin	Prothrombin Æ thrombin
F. XIII	Æ F XIIIa	Prothrombinase-komplex
F. V	Æ F Va	
F. VIII	Æ F VIIIa	
Platelet activation		
Anticoagulant action		Receptor-mediated cellular effects
Protein C	Æ protein Ca	
Receptor-mediated cellular effects		

Table 2. Thrombin-and F Xa-inhibitors

	Type	Clinical studies in
Direct thrombin inhibitors		
Hirudin	Protein	Orthopedic surgery, ACS, HIT, myocardial infarction
PEG-hirudin	PEG-coupled protein	Acute coronary syndromes, coronary angioplasty
Bivalirudin (hirulog)	Oligopeptide	Acute myocardial infarction
Argatroban	Peptidomimetic	Heparin-induced thrombocytopenia
Ximelagatran	Peptidomimetic, orally active	Orthopedic surgery, atrial fibrillation, unstable angina
Inogatran	Peptidomimetic	Myocardial infarction
Factor Xa-inhibitors		
Fondaparinux (pentasaccharide)	Glycosaminoglycan, indirect F Xa-inhibitor	Orthopedic surgery, hip fractures, PTCA
DX9065A and others	Small molecules	In phase I-II
Oral F Xa-inhibitors	Small molecules	In phase I-II

bleeding complications under hirudin were not more frequent than in the heparin group. The clinical efficacy was equivalent to or minimally better than that of heparin[15,16].

In further studies another recombinant hirudin (HBW 023) was used in patients with acute myocardial infarcts together with streptokinase[17-19]. Patients received either hirudin (IV bolus of 0.2 mg/kg, followed by 0.5 mg/kg/h as continuous infusion) or UFH. There were on significant differences in either efficacy or bleeding complications between the two treatment groups. It is possible that the observed haemorrhagic complications in the studies with higher hirudin doses were partially caused by the concomitant use of aspirin.

Interactions of hirudin and aspirin: We compared the effect of PEG-hirudin and aspirin alone with a combination of PEG-hirudin and aspirin in healthy volunteeres[20]. A mean hirudin level of 1.8. µg/mL was achieved. The bleeding time under PEG-hirudin was minimally prolonged, under aspirin slightly prolonged but very prolonged in volunteers who received 300 mg aspirin + PEG-hirudin. The effect of the combination was more than additive. We cannot yet explain what causes this synergistic effect of a combination of hirudin and aspirin.

Similar interaction studies with heparin and aspirin have shown that the combined use leads to prolongation of the bleeding time but only to a slight additive effect[21].

Hirudin in the prophylaxis and treatment of deep venous thrombosis: Hirudin has been more effective than UFH in the prophylaxis of thrombosis after total hip replacement[22]. In another large study recombinant hirudin (2 x 15 mg/day s.c.) was compared the LMWH enoxaparin (once daily 40 mg s.c.)[23]. Enoxaparin was administered to 1023 patients and hirudin to 1028 patients. The thrombosis rate in the enoxaparin group was 28.5% and in the hirudin group 18.4%. Hirudin significantly reduced the incidence of proximal thrombosis (7.5% in the enoxaparin group, 4.5% in the hirudin group). Hirudin has been approved for this indication.

Bivalirudin (Hirulog)

Bivalirudin (hirulog) a synthetic 20 aminoacid peptide has been compared with UFH in several studies in patients with PTCA and acute coronary syndromes and has shown efficacy in both indications[3,24-27]. Bivalirudin at a dose of 1 mg/kg every 8 hours was effective in a dose finding study on the prevention of thromboses after major hip or knee surgery[28].

In a recent large study (HERO-2 Acute MI Study) bivalirudin, given as IV bolus of 0.2 mg/kg, followed by 0.5 mg/kg/h for 12 hours and 0.2 mg/kg/h up to 60 hours in more than 17.000 patients receiving fibrinolytic

therapy for acute myocardial infarction. Thirty day mortality was 10.8% in the bivalirudin- and 10.9% in the heparin group. There were significantly fewer reinfarctions within 96 hours in the bivalirudin-group. Moderate and mild bleedings, however, were significantly more frequent in the bivalirudin-group[29].

Argatroban

Argatroban is a direct thrombin inhibitor that was discovered in the 1970s by Shosuke Okamoto in Japan[30,31]. Preclinical as well as pilot clinical studies have been performed and published on argatroban[32,33].

It was first clinically used in Japan in patients for treatment of peripheral arterial occlusive disease in the early1980s. Today it is approved in Japan for treatment of arterial thrombosis (1990), acute cerebral thrombosis (1996) and anticoagulation of ATIII deficient patients undergoing hemodialysis (1996). Argatroban was approved in the United States in 2000 for both prophylaxis and treatment of thrombosis associated with heparin-induced thrombocytopenia type II (HIT-II).

Argatroban is excreted through the liver and therefore does not accumulate in renally impaired patients. Argatroban can be monitored using aPTT. It is less effective than hirudin, but this fact is associated with a (probably) larger therapeutic window. Argatroban will not produce antibodies and therefore long-term and repeat treatments are possible. Argatroban can easily be monitored[34].

Preliminary studies have shown successful use of argatroban for anticoagulation during percutaneous coronary intervention in HIT II-patients without excessive bleeding[34,35].

Inogatran

Inogatran is a low molecular weight specific thrombin inhibitor that has been investigated in patients with myocardial ischaemia (TRIM study). In this study inogatran was administered intravenously, no advantage in comparison to UFH could be demonstrated[36]. After stopping the inogatran infusion a reactivation of thrombin and increased ischaemic reactions have been described[37]. The concomitant use of inogatran and aspirin did not lead to potentiation of the anticoagulant effects[38].

ORALLY ACTIVE THROMBIN INHIBITORS

Melagatran (Ximelagatran)

H376/95 the prodrug of melagatran is a small molecule (molecular weight 474 D) with a bioavailability of about 20%. The molecule is absorbed within 15-30 minutes, the highest melagatran plasma levels are reached within 1-2 hours[39-40].

In the METHRO II-study melagatran (24 mg) was compared with dalteparin in 1876 patients with total knee or hip replacement. In both patients groups melagatran was significantly more effective than dalteparin. The thrombosis incidence was almost halved in patients with total hip replacement or total knee replacement[39]. Melagatran is presently being investigated in several further large clinical trials. The future will show, whether oral thrombin inhibitors as ximelagatran are more effective or as effective as vitamin-K-antagonists with less bleeding complications.

THROMBIN INHIBITORS in the PROPHYLAXIS and TREATMENT of HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia type II (HIT II) is triggered by an immune response to heparin. For the diagnosis of HIT II a reduction of the platelet count, especially during days 3-21 after onset of heparin treatment, and clinical symptoms are more important than laboratory tests. The frequency of HIT II in different patient groups is not well established. Frequencies of 2-5% of all heparin treated patients have been described but in prospective trials on the treatment of deep venous thrombosis and also in patients undergoing vascular surgery much lower percentages have been reported[41-46]. With the increasing use of LMWHs, which leads only rarely to this complication, HIT II becomes a very rare complication.

The most dramatic and dangerous clinical complications of HIT II are venous and/or arterial thromboses. Patients with HIT II associated thrombosis have been reported to have a mortality of 25-30% and an amputation rate of up to 25%[47].

The pathophysiologic process of HIT II is associated with the generation of antibodies which bind to a complex of heparin coupled with peptides and proteins on platelet and endothelial cell surfaces[48,49]. The currently accepted hypothesis of the pathophysiology of

HIT II is based on the development of an lgG-antibody to the heparin-PF4-complex that also recognizes the FcgRIIA receptor on platelets. Binding of this complex causes platelet aggregation and thrombin generation. This concept is probably incomplete because the interactions between endothelium and antibodies are still not fully understood[50]. Endothelial cells are probably incolved in the mechanism via binding of the antibody to glycosaminoglycans on the cell surfece but also to other endothelial epitopes. Damaged endothelial cells probably are the starting point for thrombotic complications.

If HIT II is suspected by a fall in platelet count which cannot be otherwise explained and before clinical symptoms appear heparin should immediately be discontinued and a prophylactic treatment against high risk thrombosis, preferable with a thrombin inhibitor should be started.

Patients with HIT II and documented clinical thrombosis have a clear indication for anticoagulation and should be treated with a thrombin inhibitor (hirudin, argatroban). A coumarin-derivative may be initiated if the thrombin inhibitor has been given for 4-7 days. Small doses of the vitamin-K-antagonist should be used initially and the thrombin inhibiton should be continued until therapeutic levels of the vitamin-K-antagonist are documented[34,51].

INDIRECT INHIBITORS of F Xa

Danaparoid

Danaparoid (Orgaran®), mainly inhibits F Xa via activation of antithrombin and has been approved for prophylaxis of thrombosis after hip replacement surgery[52]. It was used for many years off-label for anticoagulation in HIT II-patients but is now approved for the treatment of HIT II-patients in Europe[53-55].

Fondaparinux (Pentasaccharide)

Fondaparinux is a synthetic sulfated pentasaccharide which resembles the natural minimal sequence of heparin for antithrombin binding. Fondaparinux has a molecular weight of 1764 D. It solely inhibits F Xa and has no antifactor lla-effect. Fondaparinux has been studied in several large clinical phase II and III-trials in patients with hip and knee replacement (EPHESUS, PENTATHLON and PENTAMAKS) and in patients with hip fracture surgery (PENTIFRA) fondaparinux was significantly more effective than UFH or a LMWH in these studies with a more than 50% reduction of thromboembolic events[53,54].

Other compounds with similar structure and synthetic low molecular weight inhibitors of F Xa for oral use are in different stages of development. It is hoped that they will be as effective or even more effective than vitamin K-antagonists and may not need monitoring[56,57].

OUTLOOK

For decades antithrombotic treatment was performed with vitamin K-antagonists or heparins. Today many new drugs have been developed or are in different stages of clinical research. Direct inhibitors of thrombin and F X have been effective in several indications. Other agents as oral and synthetic heparins, inhibitors of F VII and oral inhibitors of F X among many others are developed at present. It is likely that some of these new drugs will replace the conventional anticoagulants in some indications in the future. However it is not likely, that vitamin K-antagonists or heparins will be out of use during the next ten years.

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