Haemostasis and thrombosis: new developments in treatment strategies

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ABSTRACT

The pivotal studies from 2002 in the field of clinical haemostasis and thrombosis were all about the evaluation of existing or novel antiplatelet and anticoagulant strategies. Most of the new agents are specifically targeted to haemostatic pathways, which have recently been shown to be of importance *in vivo* and usually have a higher efficacy in comparison with currently available treatment strategies. In some cases this also results in a (relatively modest) increase in the risk of bleeding. The clinical use of the new compounds is often much more convenient than that of the currently available antithrombotic modalities.

INTRODUCTION

The most important published clinical studies in the field of haemostasis and thrombosis in 2002 all concern anticoagulant treatment of arterial or venous thromboembolism. One of these studies once again compares the currently widely used aspirin and vitamin K antagonists (coumarin derivatives) as secondary prevention after myocardial infarction, whereas the others relate to new antiplatelet and anticoagulant agents. The need for new anticoagulant agents is quite obvious. Firstly, the current agents are insufficiently effective. For example 10 to 15% of patients undergoing major orthopaedic surgery develop venous thromboembolism, despite prophylaxis with low-molecular-weight (LMW) heparin.[1] Furthermore, the available anticoagulants are relatively unsafe. Serious bleeding in patients treated with coumarin derivatives occurs in 1 to 2% per year, whereas in 5 to 10% per year less serious bleeding complicates this treatment.[2,3] Lastly, current anticoagulant agents are often cumbersome with regards to their clinical use, requiring repeated laboratory control and frequent dose adjustments. Increasing knowledge on the function of the haemostatic system *in vivo* has resulted in a new generation of anticoagulant agents, both directed at platelet aggregation and at inhibition of fibrin formation. Some of these new agents are now being tested in clinical phase II and III studies.

THE ASPECT STUDY

In the ASPECT (Anticoagulation in Secondary Prevention of Coronary Thrombosis Trial) study aspirin was compared with vitamin K antagonists after myocardial infarction. Both aspirin and oral anticoagulation with vitamin K antagonists are effective as secondary prophylaxis in patients after myocardial infarction or unstable angina. A head-to-head comparison of these two agents with adequate dosing and a sufficiently large sample size has so far not been performed.[4] The ASPECT-2 study addressed the issue as to which anticoagulant regimen was most effective in preventing recurrent atherothrombotic complications after an acute coronary syndrome.[2] This study included 999 patients with a previous episode of acute myocardial infarction or unstable angina. Patients were randomised to receive aspirin, high-intensity coumarin (INR 3.0-4.0),

or aspirin in combination with moderately dosed coumarin (INR 2.5-3.0). Mean follow-up was 26 months and the main outcome parameter was death, acute myocardial infarction or stroke. The incidence of this composite endpoint was significantly lower in the high-dose coumarin and moderate-dose coumarin plus aspirin group compared with the aspirin-alone group (5, 5, and 9%, respectively), resulting in a hazard ratio of about 50% (95% confidence interval (CI) 0.3-1.0) of coumarin-containing regimens versus aspirin alone. There was a nonsignificant trend towards a lower mortality in the coumarin group (1%), compared with the coumarin plus aspirin group (3%) and the aspirin-alone group (4%). The incidence of major bleeding was 2% in the group receiving aspirin plus coumarin and 1% in the two other groups. Haemorrhagic stroke only occurred in 1 of 332 patients (0.3%) in the aspirin plus coumarin group. Another salient result in this trial was again the demonstration of the poor regulation of vitamin K antagonist therapy, resulting in only about 50% of patients being in the therapeutic range for only 50% of the time, as had been shown by previous trials as well.

LONG-TERM CLOPIDOGREL AND ASPIRIN AFTER PERCUTANEOUS CORONARY INTERVENTIONS

Clopidogrel belongs to the class of thienopyridine derivatives which act by blocking the adenosine 5'-diphosphate (ADP) receptor on the platelet. A previous study comparing clopidogrel with aspirin as secondary prophylaxis in patients with a myocardial infarction, stroke or peripheral arterial disease demonstrated an equivalent efficacy of these two antiplatelet agents.[5] The combination of clopidogrel and aspirin was shown to be superior to aspirin alone in another study of patients after an acute coronary event (defined as acute myocardial infarction or unstable angina).[6] In this study of over 12,000 patients, the incidence of the combined endpoint of cardiovascular mortality, myocardial infarction or stroke was 9.3% in the clopidogrel plus aspirin group compared with 11.5% in the aspirin-alone group (relative risk 0.8, 95% CI 0.72-0.89). Earlier studies had already shown the superiority of the combination aspirin and clopidogrel in the protection against acute thrombotic occlusion of coronary stents in the first six weeks after placement in comparison with various combinations of anticoagulant agents at relatively high doses.[7] The CREDO (Clopidogrel for Reduction of Events During Observation) trial was designed to answer the question whether the combination clopidogrel plus aspirin would also offer longer-term protection against cardiovascular mortality, myocardial infarction or the need for revascularisation in patients who had been treated with intracoronary stents.[8] More than 2000 patients in 99 different centres participated in the trial. During a 12-month follow-up the incidence of the composite endpoint was 8.5% in the clopidogrel plus aspirin group and 11.5% in the aspirin-alone group, a relative risk reduction of 27% (95% CI 3.9-44.4). Major bleeding was somewhat more frequent in the aspirin plus clopidogrel group (8.8%) compared with the aspirin group (6.7%). In previous studies the incidence of major bleeding with the combination aspirin and clopidogrel was comparable with bleeding induced by aspirin alone.[5,6] Based on these results, it can be concluded that the combination aspirin and clopidogrel is a promising strategy for secondary prophylaxis of atherothrombotic events. Future studies should determine whether the additional protection offered by this combination will also be present at even longer follow-up.

DISAPPOINTING RESULTS OF ORAL GLYCOPROTEIN IIB/IIIA INHIBITION

The platelet glycoprotein (GP) IIb/IIIa receptor can bind to fibrinogen, which is the pivotal event in platelet aggregation. Competitive inhibition of this receptor is therefore theoretically the most potent antiplatelet therapy available. The prototype of GP IIb/IIIa inhibitors is the humanised monoclonal antibody abciximab. In four large trials with this compound the efficacy of abciximab in patients undergoing (complex) percutaneous intracoronary interventions, with and without stent placement, was confirmed.[9-12] Based on this success and in view of the potential disadvantages of murine monoclonal antibody therapy, and the relatively high price, a large array of alternative GP IIb/IIIa receptors have been developed. These agents are synthetic peptides, containing the sequence 'arginine-glycine-aspartamic acid (RGD)', which is essential for the interaction with the GP IIb/IIIa receptor, or peptidomimetics, which mimic this RGD sequence. Clinical trials again show a superior efficacy in patients with complex coronary revascularisation.[13,14] Subsequent studies with these agents in patients with acute coronary syndromes (acute myocardial infarction or unstable angina) were more difficult to interpret. It seems that GP IIb/IIIa inhibition is specifically successful in patients who undergo coronary interventions and is less effective, compared with standard therapy, in less complicated situations.[15] Recently, oral formulations of GP IIb/IIIa have become available, which allow long-term treatment. A number of studies have been performed with these compounds, mostly comparing oral GP IIb/IIIa inhibition with aspirin. Disappointingly, most of the studies did not show any benefit of the oral GP IIb/IIIa inhibitors and were prematurely stopped.[16-18] The reason for this

outcome is not clear but it could be that a too low systemic bioavailability after oral ingestion or a too low dose (in view of an otherwise unacceptable bleeding risk) might be a factor.[19] Also, insufficient knowledge on consequences of long-term blockade of the GP IIb/IIIa receptor might explain the unexpected result. Post-hoc analyses of the various studies even suggest a detrimental effect of GP IIb/IIIa receptor antagonists, which has led to speculation on paradoxical induction of platelet aggregation by these inhibitors.

EFFICACY AND SAFETY OF NEW THROMBIN INHIBITORS

Thrombin is the central enzyme in the coagulation process, not only mediating the conversion of fibrinogen to fibrin, but also the most important physiological activator of platelets and various other coagulation factors. Inhibition of thrombin can be achieved by administration of heparin, which potentiates the physiological inhibition of thrombin by endogenous antithrombin. In view of the limited capability of the heparin antithrombin complex to inhibit surface-bound thrombin, new antithrombin-independent anticoagulants have been developed.[20] In experimental studies the higher anticoagulant efficacy of these agents has indeed been confirmed. The prototype of these thrombin inhibitors is hirudin, originally derived from the saliva of leeches (*hirudo medicinalis*) and as such already familiar to 12th century physicians as an effective anticoagulant. Nowadays, hirudin is produced by recombinant technology. Recombinant hirudin and its derivatives have been studied extensively in a number of clinical studies, mostly in patients with acute coronary syndromes. From these studies it was concluded that these agents have a somewhat higher efficacy compared with heparin, but that major bleeding is a serious limiting factor.[21] Other practical disadvantages of hirudin and hirudin derivatives are the exclusive parenteral mode of administration and the need to regularly monitor the intensity of anticoagulation.

Recently, a new direct thrombin inhibitor has become available that has no such limitations. Melagatran is a synthetic thrombin inhibitor, which has predictable pharmacokinetic properties and can thus be used in a fixed dose.[22] Moreover, the pro-drug ximelagatran is relatively quickly absorbed after oral ingestion and results in sufficient systemic availability, rendering this agent suitable for long-term use as an oral anticoagulant. The first large clinical studies with (xi)melagatran were performed in patients undergoing prosthetic hip or knee surgery.[23,24] In several dose-finding studies the efficacy of melagatran in comparison with current antithrombotic prophylaxis (mostly low-molecular-weight (LMW) heparin) was evaluated. These studies showed an incidence of venographic thrombosis in patients who received the highest dose of (xi)melagatran at 15.1% compared with 28.2% in the LMW heparin group. This benefit was, however, only achieved at the expense of a twofold higher risk of serious bleeding (2.4% in the LMW heparin group versus 5.0% in the (xi)melagatran group). In a subsequent study in comparable patients the perioperative dose of (xi)melagatran was slightly reduced, which resulted in an equal efficacy but a lower bleeding rate (3.3%).[25] Another study demonstrated that in patients who were initially treated with the current antithrombotic agents (heparin followed by vitamin K antagonists) for six months, long-term treatment with ximelagatran resulted in a sharp decline in recurrent venous thromboembolism compared with placebo.[26] Remarkably, there was no increase in the incidence of serious bleeding during the 18-month follow-up (incidence 1% and no fatal or intracerebral bleeding). Currently, ximelagatran is being studied in the acute phase of patients with venous thromboembolism, for the prevention of cerebral infarcts in patients with atrial fibrillation, and in patients with acute coronary syndromes.

SPECIFIC FACTOR XA INHIBITION

Pentasaccharides are synthetic compounds that specifically inhibit factor Xa by selective binding to antithrombin.[27] Pentasaccharides lack the string of sulphated chains, present in about 50% of heparin molecules, which is required for inhibition of thrombin. Therefore, pentasaccharides have only specificity towards factor Xa. The agents have a good systemic bioavailability after subcutaneous administration and predictable pharmacokinetics, which makes control of the intensity of anticoagulation unnecessary. There are two pentasaccharides currently under study, fondaparinux and idraparinux. The main difference between these two agents is the elimination half-life, which is 15 to 20 hours for fondaparinux and five and a half days for idraparinux. This means that idraparinux can be administered once weekly, which renders the subcutaneous route of administration less cumbersome. After initial dose-finding studies the efficacy of fondaparinux was evaluated in two studies in patients who underwent hip replacement surgery.[28,29] In both studies the administration of fondaparinux, started postoperatively, was compared with the LMW heparin enoxaparin. The only difference between the two studies was that in one study a relatively high dose of enoxaparin was started postoperatively and in the other study a lower dose of enoxaparin was started preoperatively. The incidence of (venographic) venous thrombosis was 4.1 to 6.1% in the fondaparinux-treated patients compared with 8.3 to 9.2% in the enoxaparin group. A similar result was achieved in

subsequent studies in patients with fractured hips and in major knee surgery.[30] A pooled estimate of these studies leads to the conclusion that fondaparinux treatment results in a 55% reduction of the risk to develop postoperative thrombosis after major orthopaedic surgery compared with LMW heparin.[31] It should be mentioned, however, that these results concern venographic thrombosis, which is mostly asymptomatic and of which the clinical relevance is not clear. The risk of serious bleeding with pentasaccharides in these studies was about 1.5-fold higher. A dose-finding study of pentasaccharides for the treatment of venous thromboembolism showed the efficacy of fondaparinux and this agent is now being investigated in a phase III trial, comparing fondaparinux with LMW heparin in patients with venous thrombosis and comparing fondaparinux with unfractionated heparin in patients with pulmonary embolism. Pentasaccharides also appear to be effective in arterial thrombosis, as indicated in a study in which fondaparinux was compared with unfractionated heparin as adjunctive therapy after thrombolysis for acute myocardial infarction and in a study of unstable angina (with LMW heparin as the comparator). The long-acting idraparinux was investigated in dose-finding studies for the long-term treatment of venous thrombosis, demonstrating that a low dose of idraparinux was as effective as vitamin K antagonists in the prevention of recurrent thrombosis but was associated with less bleeding.[32] If treatment with pentasaccharides is complicated by bleeding, results from a trial in healthy subjects indicate that administration of recombinant factor VIIa is effective to reverse the anticoagulant effect.[33]

CONCLUSION

A better insight in the function of the haemostatic system *in vivo* has resulted in the development of new antiplatelet agents and anticoagulants. Initial clinical studies show that these agents often have a higher efficacy in the prevention and treatment of arterial and venous thromboembolism. The clinical applicability of most of the new agents is less demanding than with the currently available agents, for example due to more predictable pharmacokinetics, a long half-life, or an oral formulation. Results of ongoing and planned clinical trials will determine the definite position of the new generation of anticoagulants in clinical practice.

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