REVIEW ARTICLE

Drugs 2004; 64 Suppl. 1: 47-52
0012-6667/04/0001-0047/$34.00/0

Clinical Potential of Oral Direct Thrombin Inhibitors in the Prevention and Treatment of Venous Thromboembolism

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Abstract

Current antithrombotic therapies are associated with various practical limitations and risks that restrict their utility in the management of venous thromboembolism. The coagulation factor, thrombin, has been the focus of extensive investigation as a pharmacological target in efforts to improve the management of venous thromboembolism. Hirudin, desirudin, bivalirudin and argatroban are direct thrombin inhibitors that have been launched for limited indications as anticoagulants. Their usefulness for long-term prophylaxis is limited by a requirement for parenteral administration, restricted licensing and bleeding/tolerability profile. Ximelagatran – which, after oral administration, is rapidly converted to its active form, melagatran – is the first oral direct thrombin inhibitor and the first new oral anticoagulant to become available in 60 years. Clinical studies have shown that melagatran/ximelagatran, without coagulation monitoring, is effective and well tolerated for the prevention of venous thromboembolism after hip replacement and knee replacement surgery. Ximelagatran is also effective in the acute treatment of venous thromboembolism and long-term secondary prevention of recurrent venous thromboembolism, the prevention of stroke in patients with atrial fibrillation and in the prevention of cardiovascular events after myocardial infarction. Oral direct thrombin inhibitors have a promising role in the management of venous thromboembolism and other associated medical conditions.

1. Clinical Challenges of Venous Thromboembolism Prevention and Treatment

Venous thromboembolism is a disease that encompasses two conditions, deep vein thrombosis and pulmonary embolism. Asymptomatic deep vein thrombosis may precede acute pulmonary embolism, which has a high potential mortality. Venous thromboembolism presents a special challenge to the clinician because it is a frequent complication of various medical disorders and surgery. The likelihood of significant morbidity and mortality remains high even in this era of modern anticoagulation.

1.1 Anticoagulation Strategies

Thrombin has a pivotal role in haemostasis and thrombosis, and anticoagulant strategies to inhibit thrombogenesis focus on inhibiting thrombin or its generation. For nearly 60 years, the mainstays of antithrombotic treatment have been unfractionated heparin[1] and coumarin compounds, primarily

warfarin.[2] Heparin, although acting immediately, exerts its anticoagulant effect indirectly, by binding to antithrombin and thereby enhancing the ability of that protein to inhibit coagulation enzymes, particularly factor Xa and thrombin. Warfarin inhibits the vitamin K-dependent, post-translational carboxylation of certain N-terminal glutamic acid residues in prothrombin and factors VII, IX and X – a modification that endows these proteins with the ability to bind calcium ions strongly and thereby to function normally.

1.2 Limitations of Current Anticoagulation Therapies

As effective as these anticoagulants are, they have pharmacodynamic and pharmacokinetic drawbacks. Heparin, for example, must be given parenterally; it binds to a number of plasma proteins and to the vessel wall and is neutralised by platelet factor 4. In addition, the heparin–antithrombin complex is not very effective in neutralising clot-bound thrombin, and in some patients heparin causes an immunological thrombocytopenia (heparin-induced thrombocytopenia).

Warfarin acts indirectly and its antithrombotic effect only becomes apparent after 3–5 days. Thus, when patients with venous thromboembolism are being treated, warfarin must be given in conjunction with a rapidly acting anticoagulant, such as heparin. Warfarin treatment must also be stopped several days before surgery, and heparin or a related drug used in the interim. In addition, warfarin interacts with a host of other drugs and food, often making anticoagulant control difficult to achieve. Finally, use of either drug requires careful laboratory monitoring, an inconvenience for both patients and physicians.

Two additional approaches have been taken to develop new anticoagulants to overcome the limitations of unfractionated heparin and warfarin. Heparin preparations have been partially modified to produce low-molecular-weight heparins (LMWHs), which are at least as effective and as well tolerated as unfractionated heparin and are replacing it in many clinical settings.[3] As LMWHs do not bind to a significant extent to plasma proteins, they have more reproducible pharmacokinetics and can be given on a weight basis, with little or no coagulation monitoring. However, they still require subcutaneous administration, which can limit outpatient use, and there remains a risk of heparin-induced thrombocytopenia, albeit much lower than with unfractionated heparin.

In a further development, the minimal antithrombin-binding unit of heparin, a pentasaccharide called fondaparinux, has been synthesised. Fondaparinux selectively enhances antithrombin-mediated inhibition of factor Xa and, unlike unfractionated heparin or LMWH, has no inhibitory effect against thrombin as is seen with unfractionated heparin or LMWH. Fondaparinux has a long half-life of approximately 17h and is administered as a once-daily subcutaneous injection. Similar to LMWHs, it also has a predictable dose–response relationship,[4] but cannot be given orally and requires subcutaneous administration.

A second approach was to produce inhibitors that bind directly to thrombin, thereby blocking its activity. Whereas thrombin bound to fibrin is relatively protected from inactivation by the unfractionated heparin or LMWH–antithrombin complex, direct thrombin inhibitors have the theoretical advantage of being able to inhibit both clot-bound and free thrombin.[5] Four direct thrombin inhibitors, lepirudin, desirudin, bivalirudin and argatroban, are available for limited indications. Lepirudin, desirudin and argatroban are used for treatment of heparin-induced thrombocytopenia, whereas bivalirudin is approved as a substitute for heparin in patients undergoing percutaneous coronary interventions. All of these agents are given intravenously and need to be monitored using the activated partial thromboplastin time.[4]

Importantly, some members of this class of drugs (ximelagatran, dabigatran) have been developed for oral administration. Ximelagatran is the first oral direct thrombin inhibitor and is most advanced in clinical development. This drug, which is converted to its active form melagatran,

has reproducible pharmacokinetics and pharmacodynamics (reviewed by Professor Haas in this Supplement). Therefore, ximelagatran can be administered as a fixed oral dose, with no need for coagulation monitoring.

2. Clinical Studies with Ximelagatran

Thrombosis is a causative or contributing factor in many diseases, and clinical studies with ximelagatran have focused on prevention of thrombosis after major elective orthopaedic surgery (reviewed by Dr. B. Eriksson in this Supplement), treatment and long-term secondary prevention of venous thromboembolism (reviewed by Dr. H. Eriksson in this Supplement), prevention of stroke in patients with atrial fibrillation and, finally, prevention of thromboembolic events after an acute coronary event (myocardial infarction). Prevention of venous thromboembolism after orthopaedic surgery is often used as a model in the development of new anticoagulants because of the relatively high venous thromboembolism event rates, short duration of prophylaxis and the opportunity to detect and quantify bleeding (reviewed by Professor Dahl in this Supplement).

2.1 Prevention of Venous Thromboembolism in Hip Replacement and Knee Replacement Surgery

Venous thromboembolism is a common complication after major orthopaedic surgery. Studies suggest that, without antithrombotic prophylaxis, deep vein thrombosis occurs in between 40% and 84% of patients undergoing total hip replacement or total knee replacement.[6] Thromboprophylaxis with LMWHs or warfarin has significantly reduced the incidence of thromboembolic complications after these procedures.[7] Although the optimal duration of this anticoagulant prophylaxis after the surgery is not known, at least 7–10 days of treatment is recommended.

Clinical development of ximelagatran has evolved to take into account differences in regional/international clinical practice with respect to venous thromboembolism prophylaxis. In Europe, initiation of prophylaxis has usually been before operation, whereas in North America prophylaxis is usually started after operation. In the dose-finding **Me**lagatran **Thr**omboprophylaxis in **O**rthopaedic surgery (METHRO) II study[8] with ximelagatran in Europe (discussed in the review by Dr. B. Eriksson), subcutaneous melagatran was started immediately before surgery, with a second subcutaneous dose in the evening. On the morning after surgery, most patients were able to switch to oral ximelagatran treatment. The METHRO II study showed a strong dose response, and the highest dosage studied (melagatran 3mg with ximelagatran 24mg) showed a significant reduction in relative risk compared with the LMWH, dalteparin, for the prevention of venous thromboembolism in patients undergoing elective total hip or total knee replacement.

The rates of excessive bleeding (as judged by investigator) increased with increasing doses of ximelagatran, but in the highest-dose group (3mg/24mg) this was not statistically different from the rates observed with dalteparin.

The European Phase III study METHRO III[9] (discussed in the review by Dr. B. Eriksson) used melagatran 3mg and ximelagatran 24mg, but omitted the preoperative dose of melagatran; therefore treatment was initiated after surgery. The efficacy and bleeding seen with the melagatran/ximelagatran regimen were comparable to those associated with the LMWH comparator, enoxaparin (40mg once daily, preoperative initiation). Furthermore, the postoperative administration of melagatran/ximelagatran reduced the number of severe bleeding events relative to those observed in the METHRO II study. It was clear from the findings of the METHRO studies that the timing of the first dose relative to surgery can be an important factor in determining the efficacy and safety of melagatran/ximelagatran treatment. On the basis of this information, the European Phase III study **Ex**panded **Pr**ophylaxis **E**valuation **S**urgery **S**tudy (EXPRESS)[10] (discussed in the review by B. Eriksson) returned to the initiation of treatment before operation, but at a reduced dose

of melagatran (2mg, followed by 3mg the evening after surgery). In EXPRESS, ximelagatran showed a favourable reduction in relative risk compared with the reference drug enoxaparin for the prevention of venous thromboembolism. There was no difference in critical site or fatal bleeding, but investigator-judged severe bleeding was more common in the melagatran/ximelagatran group (3%) than in the enoxaparin group (1%).

Melagatran/ximelagatran has recently been approved in several European countries for the prevention of venous thromboembolism in patients undergoing total hip or knee replacement surgery, based on the post-operative (METHRO III) regimen, with the first dose of melagatran being administered 4 to 8 hours after surgery.

Two Phase III studies in North America with ximelagatran used a postoperative start of oral ximelagatran 24mg (mean time to first dose approximately 20h) and compared it with warfarin (in total knee replacement)[11] and enoxaparin (in total hip replacement, 30mg twice daily, postoperative initiation).[12] Ximelagatran was at least as effective as warfarin at preventing venous thromboembolism, whereas bleeding rates were similar. The enoxaparin comparison in total hip replacement showed low rates of venous thromboembolism with both enoxaparin and ximelagatran, although enoxaparin did show a statistically significant difference. As in the former case, the bleeding rates with the two agents were similar in this study. Subsequently, clinical development evolved to examine ximelagatran in total knee replacement, examining both 24mg twice-daily and 36mg twice-daily doses of ximelagatran in the **Ex**anta **U**sed to **L**esson **T**hrombosis (EXULT) A clinical trial,[13] and the 36mg twice-daily dose in EXULT B (both discussed by Dr. B. Eriksson).[14] In EXULT A, ximelagatran 36mg twice daily was significantly more efficacious than warfarin, with similar bleeding rates. This finding was confirmed by EXULT B, in which ximelagatran 36mg twice daily was significantly more effective than warfarin in reducing total venous thromboembolism and all-cause mortality, and showed comparable bleeding rates.

2.2 Benefits of Ximelagatran in Elective Orthopaedic Surgery

Practical experience gained with ximelagatran therapy in elective orthopaedic surgery has shown a number of potential benefits. For example, postoperative dosing with ximelagatran avoids the need for patients to be admitted the evening before surgery for prophylaxis to commence. In addition, the pharmacokinetic and pharmacodynamic profile of ximelagatran lends itself to management of patients in the prevention of venous thromboembolism, with its rapid onset and offset of action. For example, if severe bleeding occurs during prevention of venous thromboembolism, haemostasis will be restored within a short time after cessation of ximelagatran.

Ximelagatran has been studied in fixed doses for the prevention of venous thromboembolism after orthopaedic surgery. Developing the optimal dosing regimen for the drug has been a challenge, as the outcomes of total hip and total knee replacement (venous thromboembolism and bleeding) are dependent, not only on the dose, but also on the time of initiation of dosing in relation to surgery. However, the results indicate that ximelagatran (and melagatran) are effective and well tolerated in the prevention of venous thromboembolism after these two orthopaedic procedures, with postoperative initiation showing efficacy comparable to that of LMWH and low rates of bleeding.

2.3 Treatment and Long-Term Secondary Prevention of Venous Thromboembolism

Several challenges for the management of venous thromboembolism remain. Patients who have a history of venous thromboembolic events are at increased risk for recurrent events, particularly when they have other current high-risk conditions, such as malignancy, coagulation factor deficiencies or prolonged immobility. Decisions regarding the need for instigation or continuation of preventative anticoagulant treatment need to be based upon continuing assessment of the extent of the risk of recurrence of venous thromboembolism

for each individual patient, together with the risk of bleeding.

In addition to studies in patients undergoing major elective orthopaedic surgery, clinical trials in patients with acute venous thromboembolism, or at risk of recurrent venous thromboembolism, have verified that ximelagatran holds great promise for both the short-term treatment and long-term secondary prevention of venous thromboembolism.

Oral ximelagatran was studied in patients with DVT in a dose-finding study **Thr**ombin **I**nhibitor in **V**enous Thrombo**E**mbolism (THRIVE) I[15] of four doses (24mg, 36mg, 48mg and 60mg twice daily) compared with the combination of dalteparin (200 IU/kg) and warfarin (international normalised ratio of 2–3), starting from the time of diagnosis of DVT by venography until a second venogram was performed 14 days later. Regression of the thrombus occurred in 69% of the patients treated with ximelagatran or with dalteparin and warfarin, whereas progression was observed in 8% and 3% of patients, respectively. Clinical symptoms improved equally in all groups. The incidence of discontinuation of study drug because of bleeding was low, occurring in 0–1.5% of patients allocated randomly to treatment with ximelagatran and in 2.7% of those receiving dalteparin–warfarin.

The THRIVE Treatment study[16] confirmed that treatment with ximelagatran 36mg twice daily alone for the duration of a standard 6-month period of treatment was as effective as standard treatment with the LMWH enoxaparin and warfarin in the initial treatment and prevention of recurrent venous thromboembolism.

The secondary prevention of recurrent venous thromboembolism with vitamin K antagonists has been increased from 3 to 6 months during the past decade, but the need for more prolonged treatment is debated, as the reduced risk of recurrence could be outweighed by the risk of major bleeding. In the THRIVE III[17] study, it was demonstrated that, after cessation of a standard 6-month period of treatment, introduction of extended secondary prevention (18 months) with ximelagatran 24mg twice daily was highly effective compared with placebo in the prevention of recurrent venous thromboembolism.

The use of warfarin, either at low intensity (as in the Prevention of Recurrent Venous Thromboembolism trial)[18] or standard intensity (as in the Extended Low-Intensity Anticoagulation for ThromboEmbolism trial),[19] for secondary prevention of venous thromboembolism has been studied. Ximelagatran has potential advantages over warfarin in this setting because it has a low potential for interaction with other drugs and has no requirement for coagulation monitoring or dose adjustment, providing consistent and effective anticoagulation.

During longer-term use of ximelagatran (more than 35 days), transient increases in liver enzymes, mainly alanine aminotransferase, of more than 3-fold higher than the upper limit of normal have been observed in a proportion of patients. These have mostly occurred between 1 and 6 months of treatment and have resolved either spontaneously or upon discontinuation of treatment.[9,13] In orthopaedic surgery, ximelagatran has not been evaluated beyond 12 days of treatment, and increases in alanine aminotransferase were infrequent, transient and occurred more often with LMWH than with ximelagatran.[17,20]

3. Conclusions

There is currently an unmet need for an effective and well-tolerated anticoagulant that can be used for the prevention and treatment of venous thromboembolism in both short-term and longer-term clinical settings. Ximelagatran appears to fill this void. Clinical trials have shown that prophylactic use of melagatran/ximelagatran is effective and well tolerated compared with LMWHs or warfarin in patients undergoing elective orthopaedic surgery. Effective use of ximelagatran has also been demonstrated in the initial treatment and long-term secondary prevention of venous thromboembolism. The pharmacodynamic and pharmacokinetic properties of orally administered ximelagatran and subcutaneously administered

melagatran provide consistent and predictable anticoagulation. Finally, promising results from continuing investigations of ximelagatran in the prevention of stroke in patients with atrial fibrillation suggest that ximelagatran has value in a wider range of indications.

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