FRESH FROM THE PIPELINE

Dabigatran etexilate

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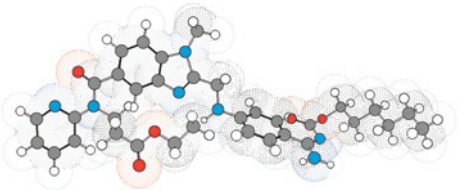

Dabigatran etexilate

In March 2008, the European Commission granted marketing authorization for dabigatran etexilate (Pradaxa; Boehringer Ingelheim), a direct thrombin inhibitor, for the prevention of venous thromboembolic events in patients who have undergone total hip- or knee-replacement surgery.

Venous thromboembolism (VTE) — occlusion of veins by blood clots — is the third most common cause of cardiovascular-associated death, after heart attacks and stroke[1]. Without preventive treatment, patients undergoing hip- or knee-replacement surgery are at high risk of developing VTE[2]. Indeed, many clinical studies have demonstrated the importance of primary thromboprophylaxis in reducing morbidity and mortality for such patients[2].

Consequently, patients undergoing orthopaedic surgery routinely receive antithrombotic therapies such as the vitamin K antagonist warfarin or heparins, which target proteases in the blood coagulation cascade[1,2] (FIG. 1a). However, although the risk of VTE persists for some time after surgery, therapy is often discontinued following discharge from hospital owing to limitations with existing drugs. Heparins are administered by injection, and warfarin, although orally administered, has a narrow therapeutic window and its activity is affected by diet and genetic makeup, and so requires careful monitoring[1]. As a result, VTE is a common cause of hospital readmission after orthopaedic surgery.

Basis of discovery

The serine protease thrombin is the final mediator in the coagulation cascade that leads to the production of fibrin, the main protein component of blood clots[1,3] (FIG. 1a). Thrombin is also a potent activator of platelets. Consequently, thrombin has been a popular target for the development of novel anticoagulants[1,3].

Several peptidic direct thrombin inhibitors (DTIs) have been approved for clinical use in the prevention of thrombosis, such as desirudin[1,3]. However, these agents still require parenteral administration, limiting their chronic use. An orally available DTI, ximelagatran (Exanta; AstraZeneca), was approved in Europe in 2004, but was subsequently withdrawn from the market owing to issues with liver toxicity. The development of other DTIs has continued, and dabigatran etexilate (FIG. 1b) is the first to receive regulatory approval in a major market.

Drug properties

Dabigatran, a potent non-peptidic DTI, was discovered using a structure-based approach starting from the crystal structure of a peptide-like DTI complexed with bovine thrombin[4]. However, it was not orally active, and so a prodrug approach was applied to modify its physicochemical characteristics[4]. This resulted in dabigatran etexilate (FIG. 1b), which showed strong and long-lasting anticoagulant effects after oral administration in animals[4,5].

Clinical data

The safety and efficacy of dabigatran etexilate was evaluated in two randomized, double-blind trials involving ~5,500 patients undergoing elective major orthopaedic surgery (one for knee-replacement surgery and one for hip-replacement surgery)[6–8]. Patients received either dabigatran etexilate (75 mg or 110 mg orally within 1–4 hours of surgery followed by 150 mg or 220 mg daily thereafter), or the low-molecular-weight heparin enoxaparin (Lovenox; Sanofi–Aventis; 40 mg as a subcutaneous injection on the day prior to surgery and daily thereafter)[6–8]. In the trial for patients undergoing knee replacement (2,076 patients), treatment was for 6–10 days[6,7], and in the trial for patients undergoing hip replacement (3,494 patients), treatment was for 28–35 days[6,8].

The composite of total VTE (including pulmonary embolism, proximal and distal deep-vein thrombosis) and all-cause mortality was the primary end point for both studies[6–8]. The results of both studies showed that the antithrombotic effect of dabigatran etexilate at doses of 220 mg and 150 mg was statistically non-inferior to that of enoxaparin on the primary end point (incidences of 6.0%, 8.6% and 6.7% in patients undergoing hip replacement, respectively, and 36.4%, 40.5% and 37.7% in patients undergoing knee replacement, respectively)[6–8]. There were no significant differences in major bleeding rates with either dose of dabigatran etexilate compared with enoxaparin in either study[6–8].

Indications

Dabigatran etexilate is approved by the European Commission for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip-replacement surgery or total knee-replacement surgery[6].

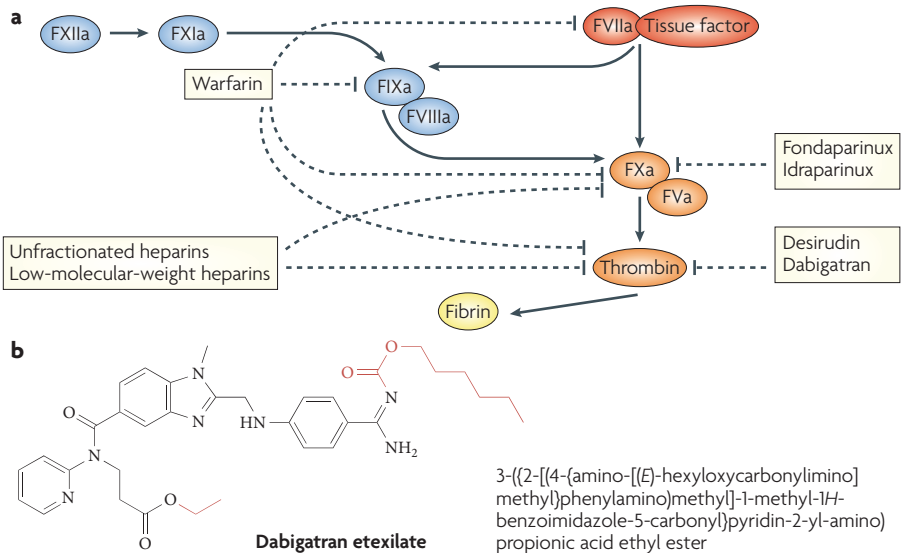

Figure 1 | **Anticoagulant drugs. a** | Simplified overview of the coagulation cascade. Points of action of selected anticoagulant drugs are shown. **b** | Dabigatran etexilate, with the prodrug groups that are hydrolysed to generate dabigatran shown in red. Part **a** is adapted from REF. 1. F, factor. ▸

ANALYSIS | VENOUS THROMBOEMBOLISM

Analysing issues in the prophylaxis of venous thromboembolism is Bengt I. Eriksson, M.D., Ph.D., Professor of Orthopaedic Surgery at the Sahlgrenska University Hospital/Östra, Gothenburg, Sweden.

For patients undergoing elective hip- and knee-replacement surgery, the current options for prophylaxis of VTE include low-molecular-weight heparin, warfarin or pentasaccharide. Guidelines advise a minimum of 10 days of treatment, with 1 month treatment recommended for those undergoing hip-replacement surgery. With shorter duration of hospital stays (mean 3–4 days), only a minority of patients actually receive the minimum 10 days of treatment. So, the burden of thromboprophylaxis has shifted from in hospital to out of hospital and to prophylactic agents that are easy to use at home.

Low-molecular-weight heparins and pentasaccharide have been shown to reduce thromboembolic events, but need to be administered subcutaneously, which may be an obstacle to optimal patient care, particularly when outpatient dosing is required after early discharge. Vitamin K antagonists, such as warfarin, have an unpredictable pharmacokinetic profile and numerous food and drug interactions, which need frequent monitoring, creating a burden for patients and health-care providers. Oral anticoagulants that require no monitoring and can be administered in a fixed dose without drug–drug and drug–food interactions would offer practical advantages over existing agents.

Thus, the focus of research efforts in the field of anticoagulant therapy over the past 15 years has been on the identification of non-peptidic, orally available, small molecules to directly inhibit the two key proteases in the coagulation cascade: thrombin and factor Xa (FXa). The recent approval of dabigatran etexilate for the prevention of venous thromboembolic events in patients who have undergone total hip- or knee-replacement surgery represents a further step forward in the care of this condition. As a once-daily oral medication without the need for coagulation monitoring, dabigatran etexilate provides greater simplicity and a welcome alternative to the daily injections that are required for low-molecular-weight heparins, the most common form of prophylaxis currently administered to patients in this setting. The pivotal trials for dabigatran etexilate showed that it was as effective as enoxaparin for the prevention of VTE, with a similar safety profile. In particular, dabigatran etexilate did not appear to demonstrate the hepatic transaminase elevations or any rebound effect on coagulation after completion of treatment previously reported with ximelagatran.

Besides dabigatran etexilate, major clinical development programmes are ongoing with different compounds targeting other specific coagulation pathways. Most of these compounds are targeted against FXa, with rivaroxaban and apixaban being agents at the most advanced stage of clinical development. Whether thrombin generation is attenuated (by FXa inhibitors) or thrombin activity is suppressed (by DTIs), the relative efficacy and safety appear to be similar. As head-to-head trials comparing FXa inhibitors with DTIs are unlikely to be conducted in the near future, these two therapeutic strategies will develop in parallel. Therefore, it is likely that the pharmacological and pharmacokinetic attributes of each individual drug may play a greater role in their clinical use.

Perhaps the greatest potential for dabigatran etexilate and the other oral anticoagulants in development is yet to come. Ongoing trials in other indications, including treatment of VTE and stroke prevention in patients with atrial fibrillation, is where these new agents will probably demonstrate their greatest advantage over existing agents, especially vitamin K antagonists. The results of these studies will contribute to improved management and quality of life for patients with various thrombotic disorders.

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doi:10.1038/nrd2622

Box 1 | Market for oral anticoagulants

Analysing the market for new oral anticoagulants are Helen Smith and Uma Yasothan, IMS Health, London, UK.

The greatest unmet need in the thrombosis market is for a new oral anticoagulant (OAC) to replace the vitamin K antagonists, such as warfarin, a class that is largely generic, with a market valued in 2007 at US$707 million globally[9]. With the brief exception of the ill-fated ximelagatran (Exanta; AstraZeneca), withdrawn in February 2006 owing to severe elevations in liver enzymes, warfarin has remained unchallenged for 50 years.

Dabigatran etexilate (Pradaxa; Boehringer Ingelheim) is a novel oral once-daily direct thrombin inhibitor that has recently been approved by the European Commission, and was launched in the UK in April 2008. It fulfils many of the requirements for a new OAC, including a predictable response with no coagulation monitoring required, an acceptable safety/toxicity profile, no drug–food interactions and a low potential for drug–drug interactions[3,6].

Dabigatran etexilate will initially be used for the prevention of venous thromboembolic events in adults who have undergone elective total hip- or total knee-replacement surgery. This indication, while representing the quickest route to market, is currently well served by the low-molecular-weight heparins such as enoxaparin (Lovenox; Sanofi–Aventis). The most valuable market for OACs is long-term therapy for the prevention of stroke in patients with atrial fibrillation, and dabigatran etexilate might achieve approval for this indication in 2010 if results of ongoing late-stage trials are positive.

However, dabigatran etexilate is also expected to face competition soon from other OACs in development, in particular rivaroxaban (Xarelto; Bayer/Johnson & Johnson). Rivaroxaban, which is most likely to be the first once-daily oral factor Xa inhibitor to be marketed, has already shown superiority to enoxaparin in major orthopaedic surgery.

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Competing financial interests
B.I.E. declares competing financial interests: see web version for details.