Commentary

Development of oral anticoagulants

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Warfarin has been the drug of choice for the prophylaxis and treatment of arterial and venous thrombotic disorders for over half a century [1]. It is the only oral anticoagulant currently approved for use in the US. Warfarin, a vitamin K antagonist, inhibits four vitamin K-dependent coagulation factors including prothrombin (factor II) and factors VII, IX and X through post-translational modification, and its anticoagulant effect is mainly due to down regulation of prothrombin and factor Xa [2]. Despite its well documented efficacy for the prevention of venous thromboembolism (VTE) after orthopaedic surgery and stroke prevention in patients with atrial fibrillation, warfarin has a narrow therapeutic window, with significant risks of haemorrhage at therapeutic concentrations. It has important limitations in clinical practice, including numerous drug and food interactions, slow onset of action, and more importantly the need for frequent laboratory monitoring to minimize the risk of inadequate anticoagulation and haemorrhagic events [3].

These limitations of warfarin have fostered a great interest in the development of novel anticoagulants for oral use to potentially replace warfarin. The design of specific inhibitors against molecular targets that play a pivotal role in the coagulation cascade has been the basis for a rational strategy for oral anticoagulant development [4]. The principal molecular targets are factor IIa (thrombin) and factor Xa. Two candidate compounds, one direct thrombin inhibitor (dabigatran etexilate developed by Boehringer Ingelheim) and one direct factor Xa inhibitor (rivaroxaban developed by Bayer), have entered phase III trials and are likely to emerge as new oral anticoagulants in the near future. A number of detailed review articles on the development of these oral anticoagulants has been recently published, shedding light on this fast growing field [5–7].

Direct thrombin inhibitor-dabigatran etexilate (BIBR 1048)

Thrombin plays a pivotal role in the coagulation cascade primarily by cleaving fibrinogen to produce fibrin clot. It also activates other coagulation factors including factors

V, VIII, XI and XIII and platelets through platelet protease activated receptors. As a result, thrombin has long been an attractive target for pharmaceutical intervention with anticoagulants either currently available, such as heparin, or in advanced stages of clinical development [4].

Before the emergence of dabigatran etexilate, ximelagatran, a prodrug for melagatran, was the first oral direct thrombin inhibitor and had proven efficacy for prevention and treatment of VTE, stroke prevention with AF and recurrent coronary events after acute myocardial infarction [8]. Although oral ximelagatran was initially approved for short-term VTE prevention in patients undergoing orthopedic surgery in Europe, it was withdrawn by AstraZeneca in 2006 due to significant hepatotoxicity. Despite its commercial demise, ximelagatran had many desirable properties as an oral anticoagulant when compared with warfarin and consistent results from clinical trials demonstrated that an oral anticoagulant specifically targeting thrombin without routine monitoring could be as effective in thrombosis prevention and as safe in terms of haemorrhage as warfarin (Table 1).

Dabigatran etexilate is a new oral direct thrombin inhibitor and the prodrug of dabigatran. Like melagatran, dabigatran is a small molecule that reversibly inhibits both free and clot-bound thrombin by binding to exosite 1 and/or the active site of thrombin [4]. The antithrombotic efficacy of dabigatran etexilate was confirmed in the first BISTRO (Boehringer Ingelheim Study in Thrombosis) study showing low DVT rates in 314 patients undergoing total hip replacement without major bleeding [16]. In patients undergoing total hip or knee replacement, dabigatran etexilate was compared with enoxaparin for the prevention of DVT or VTE in a series of trials. In the second BISTRO trial, 1973 patients were randomly assigned to dabigatran etexilate (50, 150 or 225 mg twice daily, 300 mg once daily started 1–4 h after surgery) or enoxaparin (40 mg once daily started 12 h prior to surgery) [9]. The rates of overall DVT and VTE were significantly lower in the dabigatran etexilate 225 mg group than in the enoxaparin group (13% vs.

Table 1

Pharmacokinetic parameters of oral anticoagulants

Property	Warfarin	Melagatran/ximelagatran/	Dabigatran/dabigatran etexilate	Rivaroxaban
Mechanism of action	Vitamin K antagonist	Direct thrombin inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor
Bioavailability (%)	~100	17.4–24.3	3.5–5	~80
t_{max} (h)	Slow onset	1.5–3.3	1.25–1.5	2–4
V (l kg ⁻¹)	0.14	1.98–2.53	0.86–1.0	0.77–2.50
Half-life (h)	20–60	2.4–4.6	7.3–16.4	5–9
Clearance (l h ⁻¹)	n/a	5.6–7.4	88.8–135.6	9.8–16.6
Route of elimination	Renal (92%)	Renal	Renal (80%)	Renal (66%) and faecal/biliary (28%)
Protein binding	High (99%)	Low	Low	Low
Food effect on absorption	Interacting with many foods	Little	Little	Little
Interactions with other drugs	Interacting with many other drugs	Macrolid antibiotics	Might be pH dependent	None reported
Involvement of CYP	2C9, 2C19, 2C8, 2C18, 1A2 and 3A4	None	None	n/a

24%). However, rates of major bleeding showed a significant dose-dependent increase at higher dosages of dabigatran etexilate. Three phase III trials are currently ongoing to compare the efficacy of dabigatran etexilate and enoxaparin in the prevention of DVT and VTE in nearly 8000 patients undergoing orthopaedic surgery [6].

In this issue of the Journal, Stangier and colleagues [10] report on an important missing piece in the puzzle of dabigatran development: a comprehensive evaluation of the pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate in healthy volunteers. Apart from their previous reports focusing on the single dose and population analyses [11, 12], they presented kinetic profiles of dabigatran etexilate from two clinical studies with either single or multiple rising doses. They also assessed the pharmacodynamics of this agent using various coagulation assays. Several desirable properties of dabigatran etexilate were demonstrated in their studies including a fast onset of action with median t_{max} ranging from 1.25 to 1.5 h, linear pharmacokinetics with dose proportional increase in exposure, great sensitivity and precision of thrombin time and ecarin clotting time assays to monitoring responses, and good tolerability with few bleeding events (Table 1). However, these studies did confirm an increase of mild-to-moderate bleeding events with dose. Since no antidotes or reversal agents are currently available for dabigatran etexilate, this has raised the question if dabigatran etexilate should be monitored and which assay, thrombin time or ecarin clotting time, should be used for this purpose. In addition, few drug–drug or interactions have been explored.

There is no information on the use of this agent in specific populations, such as patients with renal disease. With the completion of phase III trials, these questions could be at least partially answered.

Direct factor Xa inhibitor- rivaroxaban (BAY 59–7939)

Factor Xa is an attractive target for the design of new oral anticoagulants. This is mainly due to the unique role factor Xa plays in the coagulation cascade as a connection between the extrinsic and intrinsic pathways. Factor Xa also regulates thrombin generation via binding to factor Va followed by activation of prothrombin to thrombin. It was hypothesized that anticoagulants targeting factor Xa might be more effective than those targeting coagulation factors located lower down in the cascade, such as thrombin [4]. This concept has been partially proved when the first indirect factor Xa inhibitor, fondaparinux, received FDA approval for the prevention and treatment of VTE. Various direct factor Xa inhibitors are currently in clinical development, among which rivaroxaban (BAY 59–7939) have entered late-stage phase III trials.

Rivaroxaban is an orally available, small-molecule, active site-directed factor Xa inhibitor [13] with predictable pharmacokinetic and pharmacodynamic profiles in healthy volunteers and patients undergoing orthopedic surgery (Table 1). It has rapid onset of factor Xa inhibition 2–4 h after oral administration. After multiple dosing, the exposure of rivaroxaban is dose proportional and no accumulation has been observed. Rivaroxaban

has an approximate bioavailability of 80% and is excreted via both renal (66%) and faecal/biliary (28%) routes [14, 15]. No significant interactions between food, antacids, digoxin, aspirin, naproxen and rivaroxaban have been noted [13] suggesting that dose adjustment of rivaroxaban would not be required when these agents are concurrently administered.

The efficacy of rivaroxaban has been compared with enoxaparin in three phase II trials in patients undergoing orthopaedic surgery. Rivaroxaban was demonstrated to be potentially effective for the prevention of DVT and VTE but without a significant dose–response so that all dose groups (2.5, 5, 10, 20, and 30 mg twice daily) exhibited efficacy comparable with enoxaparin. However, with respect to major postoperative bleeding, a statistically significant dose-dependence was evident across the rivaroxaban treatment groups, with the lower dose (2.5 mg twice daily) having frequencies comparable with that observed with enoxaparin [6]. A large phase III study using one dose of rivaroxaban (10 mg once daily) is currently ongoing in over 9000 orthopaedic patients to compare rivaroxaban and enoxaparin in reducing the risk of DVT as well as assessing the safety of this agent.

Conclusions

Selective thrombin and factor Xa inhibition represents a strategy for the development of new oral anticoagulants. Compared with warfarin, they are potentially more effective, safer and easier to use due to their predictable pharmacokinetics and pharmacodynamics. Despite some concerns over bleeding and monitoring, these new agents should lead to an improved management of patients with thrombosis.

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Received

20 February 2007

Accepted

22 February 2007

Published OnlineEarly

15 May 2007

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