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The novel anticoagulants: entering a new era

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Summary

During the past five decades, anticoagulant therapy has consisted of rapidly acting parenteral drugs (unfractionated heparin [UFH] low-molecular-weight heparins [LMWH]) for prevention of venous thromboembolism and initial treatment of arterial and venous thromboembolism, whereas vitamin K antagonists (VKA) are used for longer term oral treatment. These drugs act by indirectly inhibiting several activated plasma clotting factors (UFH, LMWH) or by blocking the synthesis of some of them (VKA). In recent years, compounds that specifically block activated coagulation factor X (FXa) or thrombin have been developed. Thus, fondaparinux, and its long-acting derivative idraparinux, are administered subcutaneously. These substances inhibit F Xa indirectly via antithrombin. Small molecules have also been developed that directly block FXa (rivaroxaban, apixaban) or thrombin (dabigatran etexilate) following oral administration.

In the present review we discuss the currently available evidence supporting the use of these new anticoagulants, in particular rivaroxaban and dabigatran etexilate, in the setting of thromboprophylaxis following major orthopaedic surgery, and the broader perspectives that these new drugs may open up in the next few years.

Key words: anticoagulant treatment; dabigatran etexilate; rivaroxaban; thrombin; factor Xa

Anticoagulation today

Heparins and vitamin K antagonists (VKA) have been *the* anticoagulants for the past fifty years. Even though these drugs are well established, they are not without drawbacks and certainly do not fulfill the definition of the ideal anticoagulant (table 1). Nonetheless, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are used successfully for the prevention of venous thromboembolism (VTE) and initial treatment of arterial or venous thromboembolism. They are administered subcutaneously once or twice daily, bind to the natural inhibitor antithrombin, and inhibit activated coagulation factors, mainly thrombin and activated factor X (FXa). If the treatment needs be continued for more than a few weeks, oral VKA are usually administered to overlap and replace heparins. VKA block a late step in the synthesis of coagulation factors VII, IX, X and II (prothrombin), and their anticoagulant effect is delayed for a few days in relation to the half-life of the circulating factors. Because of the relatively long and different half-life of circulating factors, a stable level of anticoagulation cannot be reached before 4–7 days. VKA include substances with a short (acenocoumarol [Sintrom®]), intermediate (warfarin [Coumadin®], fluindione [Previscan®]) or long (phenprocoumon [Marcoumar®]) half-life. This feature, along with a genetically induced metabolic variability, the influence of environmental variables such as vitamin K content of food, and a narrow therapeutic window, require close monitoring of VKA treatment in order to maintain the International Normalised Ratio (INR) within the therapeutic range.

On the other hand, UFH must also be closely monitored when used to treat established throm-

Table 1

Characteristics of the ideal anticoagulant.

Administered orally, one tablet once daily
Highly effective in reducing thromboembolic events
Predictable dose response and kinetics
Low rate of bleeding events
No routine monitoring of coagulation or platelet count required
Wide therapeutic window
No dose adjustment required
Little interaction with food or other drugs
Low, nonspecific plasma protein binding
Inhibition of both free and clot-bound activated coagulation factors

Conflicts of interest: Consultancy: Bayer Health-Care, Pfizer; lecture fees: sanofi aventis, Glaxo Smith Kline.

boembolism, in view of wide interindividual variability in response to the doses administered, this being less the case with LMWH, which are dosed according to body weight and usually do not require laboratory monitoring to ensure efficacy and safety. Both UFH and LMWH do not require such monitoring if used in the thromboprophylactic setting. Nevertheless, platelet count needs be regularly checked due to the risk of heparin-induced thrombocytopenia.

Thus, the present anticoagulants are cumbersome to use, and there was a need to develop alternative, user-friendlier drugs, possibly with an improved benefit-to-risk profile. In the present review we briefly discuss the recently licensed parenteral indirect FXa inhibitor fondaparinux, and then focus on the upcoming new oral anticoagulants specifically targeting FXa or thrombin.

The novel parenteral anticoagulant drugs

Fondaparinux (Arixtra®, GlaxoSmithKline) is licensed as an alternative to UFH and LMWH for the prevention and initial treatment of VTE [1] as well as an anticoagulant in the setting of non ST segment elevation myocardial infarction. This synthetic pentasaccharide acts by binding to antithrombin, and specifically blocks FXa. It has been shown to be more efficacious than LMWH for prevention of VTE following major orthopaedic surgery [2], and it carries the advantages of being synthetic and of not producing heparin-induced thrombocytopenia (HIT), even though one suggestive case has been reported [3]. A long-acting derivative of fondaparinux, called idraparinux (developed by sanofi-aventis), can be injected once weekly, which has raised concerns with respect to the bleeding risk, especially in elderly patients and particularly in the absence of an antidote. Recently a biotinylated variant of idraparinux has been developed, the anticoagulant effect of which can be rapidly reversed by intravenous injection of avidin. The phase III development of idraparinux has not been as straightforward as hoped, with the VAN GOGH study failing to show non-inferiority as compared to LMWH in patients with acute pulmonary embolism [4], while the AMADEUS study was prematurely stopped due to excess bleeding in patients with atrial fibrillation [5]. Clinical studies with the biotinylated form of idraparinux (SSR12517E) are ongoing.

Figure 1

Targets of new anticoagulant drugs.
A Inhibitors of the tissue factor/factor VIIa pathway
B Specific inhibitors of factor Xa (example: fondaparinux [indirect], rivaroxaban [direct])
C Direct thrombin inhibitors (example: dabigatran etexilate)

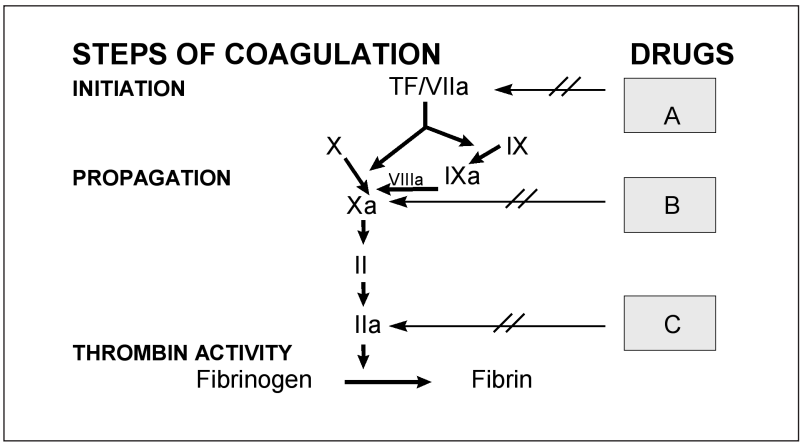

Table 2

Drawbacks of heparins (UFH and LMWH) and comparison with fondaparinux and new oral synthetic direct factor Xa or thrombin inhibitors ("new compounds").

Drawbacks of heparins	Drawback obviated with	
	Fondaparinux	New compounds
Need for antithrombin	–	+
Inability to inhibit clot-bound activated coagulation factors	+	+
Need for laboratory monitoring (except LMWH)	+	+
Heparin-induced thrombocytopenia	+	+
Lack of oral administration	–	+
Animal origin	+	+
Narrow benefit/risk ratio	*	*

"+" stands for "obviated"; "–" stands for "not obviated"; *still to be established

The novel oral anticoagulant drugs

Several new oral anticoagulants are currently under clinical development (fig. 1). These direct (i.e. antithrombin-independent) inhibitors of FXa (e.g. rivaroxaban, apixaban) or thrombin (e.g. dabigatran etexilate) are free from most of the drawbacks of heparins (table 2) and have the potential to replace both heparins and VKA in the future in a substantial proportion of patients.

A few years ago another direct thrombin inhibitor (DTI), ximelagatran (Exanta®, Astra Zeneca), had been released on the market with the indication of thromboprophylaxis following major orthopaedic surgery, but was withdrawn soon after liver toxicity had become obvious with alteration of the liver function tests in some 8% of patients if the drug was administered for a more prolonged period than simple short-term prophylaxis. At present three oral compounds are being studied in phase III clinical trials: rivaroxaban (developed jointly by Bayer and Johnson & Johnson) and apixaban (Bristol-Myers-Squibb and Pfizer), which are both direct FXa inhibitors, and dabigatran etexilate (Boehringer-Ingelheim), a DTI.

Their main characteristics are compared in table 3. Rivaroxaban and dabigatran etexilate have completed phase III development for the indication of thromboprophylaxis in major orthopaedic surgery, and have been released by the EMEA. Their introduction on the Swiss market can be anticipated before the end of this year or during the first months of 2009.

Table 3

Comparison of three upcoming novel oral anticoagulants.

	Apixaban	Rivaroxaban	Dabigatran etexilate
Type	Direct FXa inhibitor	Direct FXa inhibitor	DTI
Company	BMS / Pfizer	Bayer / Schering / Johnson&Johnson	Boehringer-Ingelheim
Half-life (hours)	8–15	5–13	14–17
Bioavailability (%)	50–85	>80	5
Elimination	25% renal 75% biliary	1/3 renal (unchanged) 1/3 renal (as inactive metabolites) 1/3 biliary	80% renal 20% biliary
Dosage	b.i.d.	o.d.	o.d. (in 2 tablets)

FXa stands for activated Factor X
DTI stands for direct thrombin inhibitor

A double prodrug, dabigatran etexilate (Pradaxa®), presents a bioavailability of 5%. Once absorbed, it is converted in the liver into its active metabolite, dabigatran. It is mainly (80%) cleared via the kidneys, which precludes its use in patients with severe renal insufficiency. This DTI has been evaluated for prophylaxis of VTE in doses of 150 or 220 mg o.d. (in two tablets) starting with a half dose 1–4 hours after surgery in patients undergoing total hip arthroplasty (RE-NOVATE study, vs enoxaparin 40 mg o.d.) [6] or total knee arthroplasty (RE-MODEL, vs. enoxaparin 40 mg o.d. [7], and RE-MOBILIZE vs enoxaparin 30 mg b.i.d. [8]). Enoxaparin was started the evening before surgery. The main results of these studies are given in table 4. In summary, non-inferiority was demonstrated versus enoxaparin 40 mg o.d., the European regimen, with the two doses of dabigatran etexilate in the RE-NOVATE study (hip replacement) and in the RE-MODEL study (knee replacement), whereas the non-inferiority criterion was not met versus the North American enoxaparin regimen of 30 mg b.i.d. in the RE-MOBILIZE study (knee replacement). Major bleedings were rare in the three studies, with no

Table 4

Dabigatran etexilate for thromboprophylaxis in major orthopaedic surgery.

Study (patients, n)	Indication	Study arms†	Main efficacy outcome*
RE-NOVATE [6] (3494)	Total hip arthroplasty	Enoxaparin 40 mg o.d.	6.7%
		Dabigatran etexilate 150 mg o.d.	8.6%
		Dabigatran etexilate 220 mg o.d.	6.0%
RE-MODEL [7] (2076)	Total knee arthroplasty	Enoxaparin 40 mg o.d.	37.7%
		Dabigatran etexilate 150 mg o.d.	40.5%
		Dabigatran etexilate 220 mg o.d.	36.4%
RE-MOBILIZE [8] (2715)	Total knee arthroplasty	Enoxaparin 30 mg b.i.d.	25.3%
		Dabigatran etexilate 150 mg	33.7%**
		Dabigatran etexilate 220 mg	31.1%

* Composite of total (venographic and symptomatic) VTE and death from all causes; unless stated otherwise, non-inferiority criteria were met for the dabigatran regimens compared to the control enoxaparin regimen
** Non-inferiority criterion not met
† All studies double-blind, with independent outcomes adjudication committee

Table 5

Rivaroxaban for thromboprophylaxis in major orthopaedic surgery.

Study (patients, n)	Indication	Study arms†	Main efficacy outcome*	NNT
RECORD 1 [9] (4541)	Total hip arthroplasty	Rivaroxaban 10 mg	1.1% (p <0.001)	38
		Enoxaparin 40 mg o.d.	3.7%	
RECORD 3 [10] (2531)	Total knee arthroplasty	Rivaroxaban 10 mg	9.6 % (p <0.001)	11
		Enoxaparin 40 mg o.d.	18.9%	
RECORD 4 [11] (2300)	Total knee arthroplasty	Rivaroxaban 10 mg	6.9% (p = 0.012)	31
		Enoxaparin 30 mg b.i.d.	10.1%	
RECORD 2 [12] (2509)	Total hip arthroplasty	Rivaroxaban 10 mg	2.0% (p <0.001)	14
		Placebo**	9.3%	

* Composite of total VTE (any DVT, non-fatal PE) and death from all causes up to the end of treatment period
** Following an initial 12-day period with enoxaparin 40 mg/day
† All studies double-blind, with independent outcomes adjudication committee
NNT stands for number needed to treat in order to avoid one event, compared to the control treatment

statistically significant difference between the arms.

Rivaroxaban (Xarelto®) is an oxazolidone derivative with more than 80% bioavailability after oral administration. It is cleared mainly via the liver (66% renal elimination) but patients with a creatinine clearance below 30 ml/min have not been enrolled in clinical trials. This FXa inhibitor has been evaluated in four phase III large-scale studies for thromboprophylaxis following major orthopaedic surgery in a dose of 10 mg o.d. starting 6 hours postoperatively. In RECORD 1 [9] and RECORD 3 [10], rivaroxaban was compared with enoxaparin 40 mg o.d. (starting the evening preceding surgery) in patients undergoing total hip (duration of prophylaxis 35 days) or knee replacement (duration of prophylaxis 12 days), respectively. In RECORD 4, the results of which were presented at the 9th EFORT congress in May 2008 [11], the comparator was the North American regimen of enoxaparin 30 mg b.i.d. in the setting of total knee replacement. Finally, RECORD 2 [12] compared a 35-day prophylactic regimen of rivaroxaban with the 12-day regimen of enoxaparin 40 mg o.d. (followed by placebo until day 35) following total knee arthroplasty. The main results of these studies are given in table 5. In fact, while RECORD 1, 3 and 4 were designed as non-inferiority trials, rivaroxaban showed statistically significant superiority to the comparator enoxaparin, irrespective of the dose regimen (40 mg o.d. or 30 mg b.i.d), with respect to the primary efficacy outcome, which was a composite of total VTE (symptomatic and asymptomatic DVT and non-fatal PE) and all-cause mortality, up to the end of the treatment duration. A feature of note, in RECORD 2 and 3, was that the symptomatic VTE events – a secondary endpoint – were also reduced by 80% and 66% respectively. Major bleedings were rare in the four studies, with no statistically significant difference between the arms.

At this stage there is no concern regarding abnormalities in liver function tests or occurrence of cardiovascular events in patients receiving dabigatran etexilate or rivaroxaban, but long-term data are scarce.

Comments and perspectives

Today, both dabigatran etexilate and rivaroxaban represent credible alternatives to the present LMWH regimens for prevention of VTE after hip or knee arthroplasty, the two surgical situations associated with the highest postoperative thromboembolic risk. Dabigatran etexilate has proved non-inferior to the European prophylactic enoxaparin regimen (40 mg daily) but not to the North American regimen (30 mg b.i.d). Rivaroxaban has shown statistically significant superiority against these two enoxaparin regimens. The two new drugs did not induce more clinically relevant bleedings than the present LMWH regimens. In addition, 35-day administration of rivaroxaban was not associated with more bleedings than 12-day administration of 40 mg enoxaparin.

Taken together, these data are very promising, and the two new compounds may soon largely replace heparins and fondaparinux for prevention of VTE following major orthopaedic surgery. Admittedly, the new drugs have not been compared with fondaparinux, which is probably the most effective (certainly not the most widely used) drug in this particular indication at the present time, but it was not registered when the studies were planned.

From a practical point of view the first administration of the two oral drugs occurs postoperatively, compared to the day before for the LMWH regimens, a change of paradigm but also a tribute to the trend towards patients being hospitalised on the day of the operation instead of the day before. Importantly, this change did not result in more thromboembolic events.

However, the ultimate goal of the new oral anticoagulants is to replace the cumbersome VKA for treatment of established VTE and for prevention of arterial embolism in patients with atrial fibrillation. These patients need longer treatment durations and represent the true challenge for the new oral compounds. Clinical trials are ongoing in these indications, which will also provide more rigorous information on potential toxicity, for the liver or otherwise.

Dabigatran etexilate and rivaroxaban target two different key enzymes in the blood coagulation system. The present data do not settle the issue whether FXa or thrombin is the best, but obviously both do work and the target may turn out to be less relevant than the dose or the timing of administration. At a later stage, head-to-head comparisons will be necessary to assess the relative benefit-to-risk ratio of the two new drugs and of the other compounds that will have been developed in the meantime [13]. In addition, their exact place in special patient populations will have to be carefully weighed, e.g. patients with reduced renal or hepatic function, pregnant women, and children. The lack of a specific inhibitor for use when urgent reversal is needed appears to be a theoretical rather than practical issue, due to the relatively short half-life of dabigatran etexilate and rivaroxaban. Nevertheless, guidelines will be required for the rare cases in which urgent reversal is necessary.

Finally, financial issues will be crucial, but cost-effectiveness analyses will have to include not only the price of the drug but also the costs that

are induced by heparins and VKA, such as laboratory costs for monitoring of anticoagulant activity and platelet count.

It is too early to predict when the parenteral anticoagulants and the VKA will be replaced by the new oral anticoagulants now approximating more and more to the definition of the "ideal anticoagulant", but the path is traced and the trend now seems irreversible.

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