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REVIEW

Early experience of the introduction of dabigatran etexilate into clinical practice

Alberto D. Delgado-Martinez

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Abstract This paper reviews the lessons learnt from the experience gained at Jaén Hospital, Spain, in the RE-MODEL™ and RE-NOVATE® trials with the oral direct thrombin inhibitor dabigatran etexilate, particularly with respect to issues relating to patient selection, dosage and treatment protocols. Dabigatran etexilate has the advantage that it does not require preoperative dosing, in contrast to injectable low-molecular-weight heparins (LMWHs) such as enoxaparin, and treatment should be started within 4 h post-surgery in patients undergoing total hip or total knee replacement. Ideally, protocols should be established to ensure that the first dose is given in the recovery room, and that subsequent doses are given at fixed times each day. If post-operative vomiting occurs, data show that the first dose can be delayed until the following day without decreased efficacy. If a patient has already been started on a LMWH, the switch to dabigatran etexilate can be made safely at the time when the next dose of LMWH would be due. Most patients can receive the standard dose (220 mg once daily), but a lower dose (150 mg once daily) is also available, which is indicated in certain subgroups, such as elderly patients and those with moderate renal impairment. Oral treatment with dabigatran etexilate has been found to be well accepted by both patients and nurses because it eliminates the need for subcutaneous injections while maintaining the efficacy and safety associated with injectable LMWHs such as enoxaparin.

Keywords Dabigatran etexilate · Dosage · Thromboprophylaxis total hip arthroplasty · Total knee arthroplasty · Venous thromboembolism

Introduction

Dabigatran etexilate is a new oral direct thrombin inhibitor that has recently been approved in Europe and many other countries for the prevention of venous thromboembolism (VTE) after elective hip or knee arthroplasty [1, 2]. Besides VTE prevention after elective hip or knee arthroplasty, dabigatran etexilate is currently being evaluated in an extensive clinical trial programme for additional indications, such as, the treatment of acute venous VTE and secondary prevention of VTE.

Prior to 2008, the only approved drugs for the prevention of VTE after elective hip or knee arthroplasty were low-molecular-weight heparins (LMWHs), fondaparinux (both of which have to be injected) and oral vitamin K antagonists (VKAs) with a target international normalized ratio of 2.0–3.0 [3]. In Europe, VKAs are used very rarely for the prevention of VTE and therefore, the majority of hip and knee patients are usually administered an injectable post-operative drug.

The RE-MODEL™ and RE-NOVATE® trials show that oral treatment with the direct thrombin inhibitor dabigatran etexilate is statistically non-inferior to subcutaneous enoxaparin in the prevention of VTE in patients undergoing elective total hip or total knee replacement, and offers a comparable safety profile in terms of major bleeding, effects on liver enzymes and major coronary events [4, 5].

This review is based on an oral presentation given by AD Delgado-Martinez at the satellite symposium entitled From Proof to Practice: Innovations in Total Hip and Total Knee Replacement, which was held during the 11th EFORT Congress, Madrid, Spain (2 June 2010).

A. D. Delgado-Martinez (✉)
Hospital San Agustin, Linares, Jaén,
Department of Orthopaedic Surgery,
Avda San Cristobal S/N,
23700 Linares (Jaén), Spain
e-mail: adelgado@ujaen.es

Jaén Hospital (Complejo Hospitalario de Jaén) enrolled more patients into these trials than any other Spanish centre, and so, the experience from this particular hospital has provided useful insights into the use of dabigatran etexilate in routine orthopaedic practice. During the course of both studies, dabigatran etexilate was found to be well received both by patients and nurses. This was largely because it avoided the need for subcutaneous injections, as such injections are often a cause of concern for many patients, as well as being laborious and time consuming for clinical staff.

This paper reviews the lessons learnt from the experience gained at Jaén Hospital in the RE-MODEL™ and RE-NOVATE® trials, particularly with respect to issues relating to patient selection and dosage of dabigatran etexilate. Similar findings have been reported in other centres in Spain, suggesting that our experience can be generalized to a broader patient population.

Patient selection

It is widely accepted that patients undergoing elective hip or knee arthroplasty should receive appropriate thromboprophylaxis, reflecting the significance of these procedures as major risk factors for VTE [3]. However, one frequent question is whether the use of dabigatran etexilate should be extended beyond these groups, to include patients undergoing revision arthroplasties, hip resurfacing procedures or hip fracture surgery. A further question is whether any specific form of anaesthesia constitutes a contraindication for dabigatran etexilate.

The pivotal trials for dabigatran etexilate investigated its use in patients undergoing elective total hip or total knee arthroplasty. Currently, dabigatran etexilate is indicated for the primary prevention of VTE in patients undergoing elective total hip or total knee arthroplasty [1]; it is not indicated for patients undergoing revision arthroplasties or hip fracture surgery as there are no clinical data for these patient populations. This criterion includes primary arthroplasties of any type (Table 1), but excludes revision procedures or hip fracture surgery because efficacy using these procedures has not yet been studied in clinical trials.

Table 1 Current indications for dabigatran etexilate [1]

Primary elective total hip arthroplasty	Primary elective total knee arthroplasty
Conventional procedures	Bi- or tri-compartmental arthroplasty
Resurfacing procedures	Minimally invasive surgery
Minimally invasive surgery	

Any form of anaesthesia can be used in patients scheduled to receive dabigatran etexilate. However, the use of dabigatran etexilate is not recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters. Once the catheter is removed, the first dose of dabigatran etexilate should be given a minimum of 2 h after removal of the catheter, and the patient monitored frequently for neurological signs or symptoms [1]. The use of other forms of invasive post-operative analgesia (such as femoral nerve blockade, intra-articular local anaesthetic infiltration or lumbar plexus blockade) with dabigatran etexilate is not restricted [1]. Indeed, femoral nerve block is a common form of post-operative analgesia for knee arthroplasty in our centre, and its use during the clinical trial (RE-MODEL™) was not associated with any specific haemorrhagic complications.

Dosing of dabigatran etexilate

In contrast to the LMWH, enoxaparin, the use of dabigatran etexilate avoids the need for preoperative dosing. In high-risk patients, such as those undergoing total hip or total knee arthroplasty, the first dose of enoxaparin must be given approximately 12 h pre-surgery [6]. This can cause problems because many patients undergoing elective hip or knee arthroplasties are only admitted to hospital on the day of the operation. In such cases, it is necessary to ask the patients to administer the injection themselves between 20:00 and 22:00 hours on the evening before surgery (a time when primary healthcare centres are usually closed). Even when patients are admitted to the hospital on the day before surgery, many centres do not have the protocols in place to ensure that enoxaparin is started preoperatively.

The first dose of dabigatran etexilate is given 1–4 h post-surgery. Treatment should be started with a single 110-mg capsule (i.e., half the normal daily dose of 220 mg) [1]. Subsequent treatment should be given once daily (220 mg), starting on the day after surgery and continuing for a total of 10 days in patients undergoing total knee arthroplasty [1] and 28–35 days in those undergoing total hip arthroplasty [1].

Dosing in patients with post-operative vomiting

The effectiveness of any oral therapy in surgical patients could be compromised by post-operative vomiting, and this may be particularly troublesome when treatment has to be started within the first hours after surgery. The scale of this problem is highlighted by the fact that almost 20% of the overall patients enrolled in RE-MODEL™ or RE-NOVATE® at Jaén Hospital experienced post-operative vomiting. Delaying the initiation of oral thromboprophy-

laxis could provide a solution to this problem because the available data suggest that such an approach is not associated with a decrease in efficacy. Evidence for this comes from a pooled analysis of the RE-MODEL™ and RE-NOVATE® studies, which examined the incidence of VTEs (proximal or symptomatic deep vein thrombosis, pulmonary embolism and death related to VTE) in patients in whom the first dose of dabigatran etexilate was delayed [7]. Overall, 178 patients (12.6%) receiving dabigatran etexilate 220 mg had their first dose delayed, compared with 1,237 patients in whom the first dose was given within 1–4 h post-surgery, as scheduled. When the first dose was delayed, the next dose was given the following morning. The incidence of major VTEs in patients receiving delayed dosing was not significantly different from that in patients in whom treatment was started at the scheduled time (Fig. 1).

In view of these findings, our current practice is to administer the first dose of dabigatran etexilate 3.5 h post-surgery (i.e., as late as possible within the recommended 4-h window). If vomiting occurs during the first 4 h after surgery, treatment is started with a full dose on the following day.

Where should the first dose be given?

A further topic relating to the first dose of dabigatran etexilate is that treatment may have to be given in different locations, depending on the patient's post-operative course; some patients may still be in the recovery room 4 h after surgery, whereas others may have already been returned to the ward. For this reason, it is important to specify after surgery the exact time at which the first dose should be given in the case notes. Alternatively, protocols should be established to ensure that all patients are kept in the recovery room for at least 4 h after surgery.

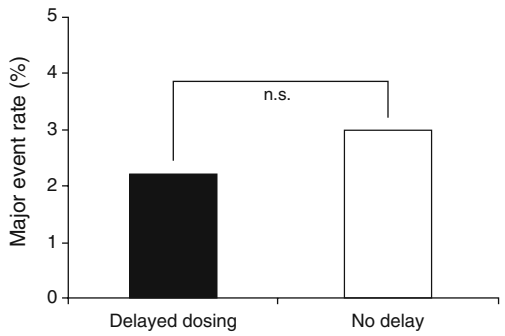

Fig. 1 Incidence of major VTEs (proximal or symptomatic deep vein thrombosis, pulmonary embolism, death related to VTE) in patients in the RE-MODEL™ and RE-NOVATE® trials in whom the first dose of dabigatran etexilate 220 mg was delayed, and those in whom treatment was started within 1–4 h post-surgery, as scheduled [7]

Timing of subsequent doses

At Jaén Hospital, routine thromboprophylactic treatment was given according to defined protocols: LMWHs were usually given at 20:00 hours every evening. If dabigatran etexilate and LMWHs are administered at different time points, this might result in a patient receiving both therapies on the same day. To avoid this, systems were put in place to try and ensure that all thromboprophylactic treatments were given at the same time.

Optimal dose of dabigatran etexilate

The RE-MODEL™ and RE-NOVATE® trials compared the efficacy of dabigatran etexilate 150 and 220 mg, with enoxaparin 40 mg [4, 5]. In the RE-MODEL™ study, which involved patients undergoing total knee replacement, treatment was continued for a median of 8 (6–10) days, whereas in the RE-NOVATE® study, in hip replacement patients, the median duration of treatment was 33 days. At the time the RE-MODEL™ trial was planned and conducted [4], the then-current American College of Chest Physicians (ACCP) guidelines (published in 2002 and 2004 [8, 9]) recommended a treatment period of 7–10 days in patients undergoing total knee replacement, and this is why a short-term regimen was adopted. Nevertheless, the more recent ACCP guidelines [3], which were published in 2008, indicate that treatment should be extended beyond 10 and up to 35 days. Indeed, the current practice in our country, and in many other European countries, is to extend the thromboprophylaxis to between 28 and 35 days.

In the RE-MODEL™ and RE-NOVATE® studies, both doses of dabigatran etexilate were statistically non-inferior to enoxaparin, and hence, both can be recommended for routine use in these patient groups. More specifically, 220 mg dabigatran etexilate is the standard dosage and recommended for most patients, whereas the lower dose (150 mg dabigatran etexilate) is recommended for certain patient subgroups, such as elderly patients and those with moderate renal impairment (Table 2) [1]. The lower dose should also be used in patients who are receiving the P-glycoprotein inhibitors amiodarone or

Table 2 Dosage recommendations for dabigatran etexilate [1]

Standard dose (220 mg/day)	Low dose (150 mg/day)
Most patients	Elderly patients (>75 years)
	Patients receiving amiodarone or verapamil
	Patients with moderate renal impairment (creatinine clearance 30–50 ml/min)

verapamil because dabigatran etexilate is a substrate for this transporter protein [1].

Adverse events reported with dabigatran etexilate are quite rare and similar to the adverse events reported with enoxaparin. To date, more than 10,000 patients have been treated in four actively controlled VTE prevention trials [4, 5, 10, 11]. As expected with any anticoagulant, the most commonly reported adverse reaction (when data from two pivotal VTE prevention studies [RE-NOVATE®, RE-MODEL™] were combined) was bleeding, which occurred in approximately 15% of patients; the frequency of major bleeds (including wound site bleeding) was less than 2.5% and did not differ from enoxaparin [7]. The experience in our hospital is in line with the adverse events described in the analysis of the results of the clinical VTE prevention trials. The majority of adverse events we observed were mild haemorrhage, anaemia or wound complications; most of which were related to surgery.

Contraindications

Dabigatran etexilate is contraindicated in patients receiving concomitant quinidine, since it is an intense inhibitor of P-glycoprotein, although this drug is not widely used [1]. Severe renal impairment (creatinine clearance <30 ml/min) is also a contraindication; LMWH is permitted for use in these patients, however a dosage adjustment is required [6]. Dabigatran etexilate is contraindicated in patients with hepatic impairment or liver disease that is expected to have an impact on life expectancy. As patients with hepatic insufficiency (elevated liver enzymes >2 times upper limit of normal in preoperative testing) were excluded from the controlled clinical trials, the use of dabigatran etexilate is not recommended in this patient population [1]. Alanine transaminase should be measured as part of the standard preoperative evaluation. As with any other anticoagulant, if there is a high risk of haemorrhage for any reason, the drug should not be given. Although in common practice, contraindications affect a very small proportion of patients, all contraindications should be ruled out during the preoperative evaluation.

Conclusions

The experience from patients treated with dabigatran etexilate in the RE-MODEL™ and RE-NOVATE® trials at Jaén Hospital shows that dabigatran etexilate provides effective, well-tolerated and well-accepted thromboprophylaxis in patients undergoing total hip or total knee replacement surgery. Oral administration of dabigatran etexilate has been particularly well received by both patients and nurses, as it avoids the need for subcutaneous injections.

Dabigatran etexilate should be used as first-line thromboprophylaxis in these patients and started on the day of surgery as described above. Ideally, treatment protocols should be established to ensure that the first dose is given in the recovery room with subsequent doses given at fixed times each day. If a patient has already started treatment with a LMWH, the switch to dabigatran etexilate can be made safely at the time when the next dose of LMWH would be due [1].

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Conflict of interest The author declares no conflict of interest.

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