Ximelagatran in Orthopaedic Surgery

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Ximelagatran · Melagatran · Orthopaedic surgery · Venous thromboembolism · Oral direct thrombin inhibitors · METHRO trials

Abstract
Ximelagatran represents the first new oral anticoagulant since the introduction of warfarin almost 60 years ago, and has been evaluated for the treatment and prevention of a range of venous and arterial thromboembolic disorders. The MElagatran THRomboprophylaxis in Orthopaedic surgery (METHRO) and EXPanded PProphylaxis Evaluation Surgery Study (EXPRESS) studies have investigated the efficacy and safety of subcutaneous (s.c.) melagatran followed by oral ximelagatran in preventing venous thromboembolism (VTE) in patients undergoing total hip replacement or total knee replacement. In METHRO II, immediate pre-operative-initiated s.c. melagatran followed by post-operative ximelagatran dose-dependently reduced VTE, with the highest dose (melagatran 3 mg/ximelagatran 24 mg twice daily) associated with a significantly reduced incidence of VTE compared with the low-molecular-weight heparin (LMWH) dalteparin (15.1 vs. 28.2%; p < 0.0001). In METHRO III, the efficacy of s.c. melagatran 3 mg/ximelagatran 24 mg twice daily initiated post-operatively (4–12 h after surgery) was comparable to that of the LMWH enoxaparin initiated 12 h before surgery (total VTE incidence, 31.0 and 27.3%, respectively). Rates of severe bleeding were also comparable between treatments (melagatran/ximelagatran = 1.4%; enoxaparin = 1.7%). Treatment with melagatran/ximelagatran was significantly more effective when initiated earlier (4–8 h) rather than later (8–12 h) after surgery (total VTE incidence, 27.5 vs. 35.4%; p = 0.0034). Based on the results of METHRO II and III, the EXPRESS study evaluated the efficacy and bleeding profile of s.c. melagatran 2 mg immediately before surgery, followed by s.c. melagatran 3 mg on the evening of the day of surgery and then ximelagatran 24 mg twice daily. This regimen was significantly more effective than enoxaparin (total VTE incidence, 20.3 vs. 26.6%; p < 0.0004). Excessive bleeding (as judged by the investigator) was more frequent with melagatran/ximelagatran, but rates of fatal bleeding, critical-site bleeding and bleeding requiring re-operation did not differ between the groups. Taken together, the METHRO and EXPRESS studies demonstrate that melagatran/ximelagatran has comparable or superior efficacy to LMWHs in the prevention of VTE in orthopaedic surgery patients, and that the timing and dose of melagatran is important in optimizing the balance of efficacy and bleeding risk.

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**Introduction**

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), and is an important cause of morbidity and mortality [1], particularly after certain surgical procedures [2]. Patients undergoing major elective orthopaedic surgery (such as hip or knee replacements) have a particularly high risk of developing VTE. Without anticoagulant therapy, VTE occurs in 40–60% of patients undergoing hip replacement surgery and 40–80% of knee replacement surgery patients [3]. Prophylaxis with either vitamin K antagonists (VKAs; such as warfarin) or low-molecular-weight heparins (LMWHs) is widely used, but both have disadvantages. VKAs have a slow onset of action, interact with numerous foods and drugs, and require frequent monitoring of coagulation and dose adjustment [4]. The LMWHs must be given subcutaneously and are associated with a higher rate of bleeding at the surgical site than VKAs, particularly if therapy is initiated soon after surgery [3].

**From Leeches to Ximelagatran: A Journey of Discovery**

Consequently, the development of new anticoagulant agents has been pursued in an attempt to meet the medical need for an oral agent with good efficacy balanced against an acceptable bleeding risk, and without the need for coagulation monitoring. Given its important role as the final common mediator of the coagulation cascade and its potent activation of platelets, thrombin has been identified as a target for new anticoagulant agents. The development of direct thrombin inhibitors (DTIs) has its origins in the discovery of the anticoagulant agent hirudin in the salivary glands of the medicinal leech Hirudo medicinalis in the 1880s [5]. The potential of hirudin as an antithrombotic agent was first investigated in the 1920s [6], but it was only in the 1990s that hirudin was introduced into clinical use. This in part reflects developments in recombinant DNA technology, with expression of recombinant hirudin in the yeast Saccharomyces cerevisiae [7] greatly simplifying large-scale production compared with extraction of hirudin from leeches. Subsequently, various synthetic DTIs have been developed, including the bivalent heparin analogue bivalirudin [8], and the small, active-site-directed inhibitors argatroban [9] and efegatran [10]. Theoretical advantages of the DTIs over the heparins include low levels of binding to plasma proteins and the ability to inhibit both free and clot-bound thrombin [11]. The results of a study of patients undergoing total hip replacement, in which recombinant hirudin was significantly more effective than the LMWH enoxaparin in preventing VTE (relative risk reduction, 28%; \( p = 0.001 \)) [12], suggest that these theoretical advantages can translate into clinical benefits. However, the need for parenteral administration has been an important limitation to the use of DTIs in routine clinical practice.

Ximelagatran is the first oral agent in the new class (World Health Organization ATC classification) of DTIs, and is the first new oral anticoagulant to be introduced into clinical practice since warfarin nearly 60 years ago. The development of ximelagatran is beyond the scope of the present article, but readers are referred to a recent review of this subject by David Gustafsson and colleagues [13]. Ximelagatran is rapidly absorbed and bioconverted to its active form, melagatran [14], which is available for subcutaneous (s.c.) administration.

**Prevention of Venous Thromboembolic Events in Elective Hip or Knee Replacement Surgery: Clinical Trials of Melagatran/Ximelagatran**

The efficacy and safety of melagatran/ximelagatran in the prevention of VTE in patients undergoing elective hip or knee replacement surgery has been investigated in three phase III clinical trials conducted in Europe – the Methagran THRomboprophylaxis in Orthopaedic surgery (METHRO) II [15], METHRO III [16] and EXPanded PRophylaxis Evaluation Surgery Study (EXPRESS) [17] studies (METHRO and EXPRESS also recruited patients from the Republic of South Africa) – and in two studies in North America [18, 19]. The optimal time to initiate anticoagulant treatment in major orthopaedic surgery continues to be debated [20, 21]. Given that deep vein thromboses can start to form during surgery itself [22], preoperative initiation of prophylaxis may have benefits in terms of efficacy. However, the risk of bleeding during surgery and of neuraxial bleeding after spinal anaesthesia may be lower with postoperative initiation. Therefore, the METHRO and EXPRESS studies were also designed to compare the efficacy and safety of melagatran/ximelagatran when initiated at different times before or after surgery.

The designs of the METHRO II, METHRO III and EXPRESS studies were similar (fig. 1) [15–17]. All were randomized, double-blind studies of melagatran/ximelagatran, with VTE as the primary efficacy end point and
severe bleeding, defined as critical-site (intracranial, intraocular, intraspinal or retroperitoneal) or excessive bleeding as judged by the investigators, as the primary safety end point.

**METHRO II**

METHRO II was a dose-response trial of melagatran/ximelagatran with a primary efficacy end point of total VTE (proximal and distal DVT, PE and VTE-related death) [15]. Patients received s.c. melagatran (1, 1.5, 2.25 or 3 mg twice daily) started immediately before surgery, followed by oral ximelagatran (8, 12, 18 or 24 mg twice daily) started the day after surgery. A control group received the LMWH dalteparin (5,000 U/day) started the evening before surgery. The initiation of melagatran immediately before surgery was based on the findings of studies with recombinant hirudin of similar design, which demonstrated that initiation of DTI therapy immediately before surgery was effective in the prophylaxis of VTE [12, 23–25]. Total duration of melagatran/ximelagatran
or dalteparin treatment was 8–11 days (see fig. 1). Patients then received a mandatory venogram, followed by 4–6 weeks of follow-up [15].

There was a significant (p = 0.0001) dose-dependent reduction in the incidence of VTE with melagatran/ximelagatran (fig. 2) that was consistent across both total hip replacement and total knee replacement surgery. At the highest dose tested (3 mg/24 mg) melagatran/ximelagatran was significantly more effective than dalteparin (total VTE incidence, 15.1 vs. 28.2%; p < 0.0001). Rates of excessive bleeding ranged from 1.1 to 5.0% with melagatran/ximelagatran compared with 2.4% in the dalteparin group, with no significant difference between dalteparin and the highest dose of melagatran/ximelagatran (3 mg/24 mg) [15].

**METHRO III**

While METHRO II considered preoperative initiation of treatment with melagatran/ximelagatran, METHRO III was designed to evaluate the efficacy and safety of postoperative initiation in the prophylaxis of VTE. Based on the results of METHRO II showing superior efficacy combined with an acceptable safety profile at the highest dose tested, METHRO III compared a single dosing regimen of melagatran/ximelagatran 3 mg/24 mg twice daily with the LMWH enoxaparin. The primary efficacy end point was subdivided into two stages of analysis: total VTE (DVT, fatal or non-fatal PE or unexplained death) and major VTE (proximal DVT, fatal or nonfatal PE or unexplained death). Melagatran 3 mg was started 4–12 h after surgery and was followed by ximelagatran 24 mg twice daily. In the control group, prophylaxis with s.c. enoxaparin (40 mg once daily) was started 12 h before surgery, in line with European clinical practice guidelines for the use of LMWHs [16].

When melagatran/ximelagatran 3 mg/24 mg was initiated postoperatively, the incidence of total VTE was 31.0%, compared with 27.3% with preoperative enoxaparin, a difference of 3.7% in favour of enoxaparin (p = 0.053). The incidence of major VTE was comparable between the treatment groups (melagatran/ximelagatran 5.7% and enoxaparin 6.2%), as was the risk of bleeding [16].

![Fig. 2. METHRO II: dose-response effect for DVT, proximal DVT and PE per treatment group for all patients undergoing total hip or total knee replacement. * for dose response; † for pairwise comparison. Reprinted with permission from Elsevier [15].](image-url)
The Importance of Timing: Initiation 4–8 Hours Postoperatively Is More Effective than 8–12 Hours after Surgery

A post hoc analysis of the data from METHRO III evaluated the efficacy and safety of postoperative initiation of melagatran/ximelagatran by the timing of the first melagatran injection. According to the METHRO III study protocol, melagatran was to be initiated 8 ± 4 h after surgery. For the post hoc analysis, patients in the melagatran/ximelagatran group were categorized according to whether melagatran was first administered from 4 to <8 h (4–8 h) or from ≥8 to 12 h (8–12 h) after surgery.

The incidence of major VTE did not differ significantly with the time treatment was initiated (fig. 3A). However, initiation of treatment closer (4–8 h) to surgery was significantly more effective than later initiation (8–12 h) in the prevention of total VTE (fig. 3B) (total VTE incidence, 27.0 vs. 35.4%; p = 0.0034) [16]. The incidence of severe bleeding was slightly higher when treatment was initiated 4–8 h (1.60%; 95% CI, 0.83–2.78) as compared with 8–12 h (1.23%; 95% CI, 0.53–2.41) after surgery (fig. 3C), but comparable to preoperative initiation of enoxaparin.

EXPRESS

EXPRESS aimed to expand on the METHRO studies using a modified version of the METHRO II study design for preoperative initiation of prophylaxis (fig. 1) [17]. The main efficacy end points were major VTE (proximal DVT, PE and/or death where PE could not be ruled out) and total VTE (distal or proximal DVT, PE and/or death from any cause) and, as in the METHRO studies, the primary safety end point was bleeding. S.c. melagatran was started immediately before surgery at a dose of 2 mg, followed by a further 3 mg dose after surgery (at least 8 h after the initial dose) and then oral ximelagatran 24 mg twice daily starting the day after surgery for 8–11 days. The control group started enoxaparin 12 h before surgery and continued on enoxaparin for 8–11 days [17].
In the EXPRESS study, melagatran/ximelagatran initiated immediately preoperatively was significantly more effective than enoxaparin in preventing VTE. Compared with enoxaparin, melagatran/ximelagatran was associated with significantly lower rates of both major VTE (2.3 vs. 6.3%; \( p < 0.0001 \)) and total VTE (20.3 vs. 26.3%; \( p < 0.0004 \)). The incidence of severe bleeding was higher with melagatran/ximelagatran (3.3%; 95% CI, 2.4–4.4) than enoxaparin (1.2%; 95% CI, 0.7–1.9). In both treatment groups, cases of severe bleeding predominantly reflected excessive bleeding as judged by the investigator and there were no cases of critical-site bleeding in either group [17].

**Fig. 4.** Combined analysis of the METHRO II, METHRO III and EXPRESS studies for the incidence of total VTE (**A**) and severe bleeding (**B**) in patients undergoing total hip or total knee replacement surgery.

**Combined Analysis of the METHRO and EXPRESS Studies**

Combined analysis of the results from METHRO II, METHRO III and EXPRESS illustrates the importance of the dose and timing of initial melagatran therapy to the balance of efficacy to safety in the prophylaxis of VTE in major orthopaedic surgery [26]. Comparable efficacy to LMWH therapy and the lowest rates of bleeding were seen with postoperative initiation of melagatran/ximelagatran in the METHRO III study (fig. 4). Administration of the first dose of melagatran 4–8 h as compared with
8–12 h after surgery optimized the balance of efficacy and safety (fig. 3). The doses of melagatran/ximelagatran that gave enhanced efficacy over LMWH when initiated preoperatively also increased the risk of bleeding compared with LMWH treatment. The risk of severe bleeding was lower with preoperative melagatran at a dose of 2 mg followed by melagatran 3 mg immediately after surgery and then oral ximelagatran 24 mg twice daily (EXPRESS) than with immediate preoperatively initiated melagatran 3 mg twice daily followed by oral ximelagatran 24 mg twice daily (METHRO II: 3.3 vs. 4.8%; fig. 4B) [26]. The majority of the reports of severe bleeding involved excessive bleeding as judged by the investigator.

The combined results also indicate almost identical rates of total VTE in patients receiving either dalteparin or enoxaparin. Therefore, the efficacy of these two regimens appears to be comparable when administered according to standard European regimens.

Conclusions

Treatment with melagatran/ximelagatran has been studied in more than 8,000 elective total hip and total knee replacement patients and was comparable or superior in efficacy to LMWH. The safety of melagatran is comparable to that of LMWH when treatment starts postoperatively, while initiating melagatran preoperatively is associated with relatively higher rates of excessive bleeding. Indeed, the METHRO II, METHRO III and EXPRESS studies showed that the timing and dose of melagatran is important in determining optimal efficacy and safety. Preoperative initiation of treatment provides superior efficacy to standard LMWH therapy, while the lowest rates of bleeding were achieved when treatment was started postoperatively. When treatment is initiated postoperatively, administration of the first melagatran dose sooner (4–8 h) rather than later (8–12 h) after surgery appears to be important to optimize prophylactic efficacy. After the initial s.c. dose of melagatran, ximelagatran brings the convenience of oral administration to the prevention of VTE in the days after surgery. Postsurgical initiation of melagatran/ximelagatran also means that patients do not need to be admitted to hospital the day before surgery solely to allow initiation of VTE prophylaxis.

Ximelagatran is the first new oral anticoagulant in nearly 60 years and offers a number of clinical benefits over other available anticoagulants. Ximelagatran provides the convenience of oral dosing using fixed-dose regimens and without coagulation monitoring. Unlike VKAs such as warfarin, ximelagatran has a rapid onset and offset of action [27] that simplifies management when initiating or stopping therapy. There is growing evidence supporting the benefit of extended prophylaxis in reducing the incidence of VTE after orthopaedic surgery [28, 29]. The availability of oral anticoagulants such as ximelagatran may be particularly important if extended prophylaxis after hip or knee replacement surgery is adopted as standard practice in the future.

References

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