pagepress
Italian Journal of Medicine 2013; volume 7:179-182

Clinical experience with fondaparinux in antiaggregate patients undergoing total hip and knee arthroplasty

Guido Grappiolo,[1] Marco Scardino,[1] Giuseppe Mazziotta,[1] Stefano Quaini,[2] Corrado Lodigiani,[1] Matteo Carlo Ferrari[1]

[1]Department of Orthopedic Surgery, Istituto Clinico Humanitas, Rozzano, Milano; [2]Department of Anaesthesiology, Ospedale Pietra Ligure, Savona, Italy

ABSTRACT

Patients undergoing total hip arthroplasty or total knee arthroplasty have a high risk for post-operative venous thromboembolism. The current study addressed the use of fondaparinux post-operatively in 556 patients with antiplatelet therapy in order to prevent deep vein thrombosis as well as demonstrate efficacy in preventing arterial thrombotic events. Results provided evidence for a safe and effective prophylaxis strategy, involving the change from low molecular weight heparin pre-operatively to fondaparinux post-operatively. Also, fondaparinux proved effective as a unique post-operative therapy in the prevention of venous thromboembolism with no adverse effects, such as major bleeding or arterial thrombosis in patients with pre-operative antiplatelet therapy.

Introduction

Patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) have a high risk for post-operative venous thromboembolism (VTE). The prevalence of venographic deep vein thrombosis (DVT) ranges from 40-85% after THA or TKA for patients without prophylaxis therapy.[1] The 8th Edition of the American College of Chest Physicians Guidelines strongly recommends the use of either fondaparinux, a low molecular weight heparin (LMWH), or a vitamin K antagonist in the prevention of VTE after major orthopedic surgery.[1]

Fondaparinux is a synthetic pentasaccharide that acts as a specific inhibitor of factor Xa without direct inhibition of thrombin. The antithrombotic activity of fondaparinux is due to its selective binding to antithrombin III.[2] This inhibition of factor Xa via antithrombin results in effective inhibition of thrombin generation.[3-6] In a dose-ranging study of fondaparinux for the prevention of VTE in patients undergoing THA, 0.75 to 8.0 mg fondaparinux once-daily, starting 6 (±2) h post-operatively, demonstrated a statistically significant dose response; the rate of venous thromboembolism was lower with the once-daily 1.5 mg and 3.0 mg doses than with 30 mg of enoxaparin given every 12 h.[7] Moreover, recent studies of patients undergoing THA or TKA surgery suggested that a once-daily subcutaneous injection of 2.5 mg fondaparinux reduced the risk of VTE more than the LMWH dose.[8-11] A meta-analysis of fondaparinux phase III data (n=5385) showed that in patients who have had major orthopedic surgery, fondaparinux reduced the incidence of VTE by 55.2% compared with enoxaparin (6.8% *vs* 13.7%, 95% confidence interval: 45.8-63.1%; P<0.001).[12]

Fondaparinux is 100% bioavailabile within 2 h of the plasmatic peak.[2] It is administered subcutaneously once daily in fixed doses without laboratory monitoring.[13] After subcutaneous injection, fondaparinux is rapidly and completely absorbed. The drug does not bind to plasma proteins[2] and is eliminated in the urine.[14] The exposure to the drug is exponentially higher in patients with renal impairment than in patients with normal renal function.[15] Research on thrombus formation both arterially and venously affirms the absolute dependence on thrombin; blocking thrombin demonstrates effectiveness in preventing the formation of vascular thrombi. Fondaparinux is more effective in preventing thromboembolic complications than other

Correspondence: Marco Scardino, Department of Orthopedic Surgery, Istituto Clinico Humanitas, Rozzano, Milano, Italy.
Tel. +39.335.5865750.
E-mail: marco.scardino@libero.it

Key words: fondaparinux, antiplatelet therapy, postoperative venous thromboembolism prophylaxis, total hip arthroplasty, total knee arthroplasty.

Conflict of interests: the authors declare no potential conflict of interests.

Acknowledgments: the Authors thank the *Fondazione Livio Sciutto,* Pietra Ligure, Savona, Italy, for its support.

Italian Journal of Medicine 2013; 7:179-182
doi:10.4081/itjm.2013.179

anticoagulant drugs due to greater selectivity in blocking the formation of fibrin clots by inhibiting the stabilizing role of platelets and/or blocking its amplification due to the fragments of fibrinogen.[6,14]

The current study addressed the use of fondaparinux in selected patients with antiplatelet therapy as a unique antithrombotic therapy.

Materials and Methods

This single-center, open-label, prospective clinical trial was approved by the Head of the Department for a limited period. All patients who satisfied the inclusion criteria and did not meet any of the exclusion criteria were offered enrollment between September 2006 and March 2009. During this period, 556 patients with low risk for cardiac or cerebral events and eligible for surgery with the indication for THA or TKA were selected to receive antiplatelet therapy due to secondary prophylaxis. All patients were selected according to the service cardiology center and the antitrombotic center of the institute.

Elective surgery exclusion criteria included: patients in a double antithrombotic therapy, cardiac or cerebrovascular instability, accidents <12 months previously, surgical indication followed by vascular surgery, known hypersensitivity to fondaparinux, age <18 years, infectious arthritis, severe renal impairment (creatinin clearance <30 mL/min), active ulcerative gastrointestinal disease or active clinically significant bleeding, congenital or acquired bleeding disorders (*e.g.* platelet count $<50\times10^9$/L), recent intracranial hemorrhage as well as recent brain, spinal or ophthalmic surgery, low body weight (<50 kg), chronic or acute DVT within seven days before surgery as determined by ultrasonography examination, technically inadequate ultrasonographic examinations, liver impairment.

All patients signed a written informed consent form describing the surgical and anesthetic type of medical and surgical treatment. The study was performed in accordance with the Declaration of Helsinki.

The patients were divided into four groups: 291 THA, 90 TKA, 35 revision TKA, and 145 revision THA. All patients received continuous epidural-spinal anesthesia with an epidural catheter from the day of surgery to at least 2 h before the first injection of fondaparinux postoperatively. All patients received paracetamol, oxycodon and COX2 for post-operative analgesia.

To prevent thromboembolism, patients were treated with the following protocol.

Change from acetylsalicylic acid (ASA) to LMWH seven days before surgery (10 days if the patient took ticlopidine). LMWH subcutaneous administration the day after the suspension of antiplatelet therapy until the night before surgery (4000 UI or 6000 UI, depending on weight). Fondaparinux was given 6-12 h after surgery, and the second dose 18-24 h after the first. All patients received anticoagulant therapy for the next 35 days and subsequent resumption of therapy prior to surgery. All patients filled a pre-donation blood bag of 350-400 mL. Hemoglobin and hematocrit values were evaluated. Patient follow up consisted of clinical evaluation, and blood chemistry analysis and review until discharge.

All patients were encouraged to perform exercises in bed immediately after surgery, and patients were allowed to walk in the physiotherapy department on Day 2 post surgery. Outcome measures included the incidence and time course of symptomatic DVT and arterial thrombosis safety end points up to 35 days after surgery. The primary safety outcome was the incidence of major or minor bleeding. The bleeding index was also calculated as follows:

$$\text{Bleeding Index} = \text{Units of RBCs} \times [1\backslash (\text{Hb before} - \text{Hb after})]$$

Fondaparinux was discontinued if any of the following occurred: major bleeding, transfusion of more than 2 packed red blood cells or whole blood transfusion or anemia (a decrease in hemoglobin of >3 g/dL from Day 1).

Results

Five-hundred and fifty-six patients without detected DVT and pulmonary thromboembolism were enrolled in the clinical study (Table 1). No patient had

Table 1. Baseline characteristics of patients undergoing total hip arthroplasty, total knee arthroplasty and revision surgeries.

	Characteristics			
	THA (n=291)	TKA (n=90)	R-THA (n=145)	R-TKA (n=35)
Age, median (range)	67.8 (54-87)	73.8 (63-82)	72.6 (64-83)	71.6 (62-79)
Gender (M/F)	96/195	35/55	26/119	5/30
BMI (kg/m^2), median (range)	23.5 (15.7-34.4)	26.0 (19.2-34.0)	24.2 (17.1-33.8)	25.2 (18.7-33.9)

THA, total hip arthroplasty; TKA, total knee arthroplasty; R-THA, revision THA group; R-TKA, revision TKA group; M, male; F, female; BMI, body mass index.

fatal bleeding, bleeding in a critical organ, or bleeding leading to re-operation in our treatment groups. Major bleeding during the treatment period was one of the primary safety end points in fondaparinux patients. There were 4 minor bleeding events (1.4%) among the 291 patients for the THA group; 1 minor bleeding event (1.1%) among the 90 patients for the TKA group; 2 minor bleeding events (1.4%) among the 145 patients for the revision THA group; no bleeding events among 35 patients for the revision TKA group. The other primary safety end point did not reveal any vascular accidents post-operatively with regards to thrombotic events (*i.e.* heart attack or electrocardiographic S-T under level curve, stroke, lower limb ischemia).

Fondaparinux did not result in any of the following complications: content of the subcutaneous suction drain, post-operative transfusion, change in hematocrit or hemoglobin levels, wound problems (blistering, hematoma, dehiscence, superficial or deep infection) or secondary intervention (ranging from aspiration to surgery). The changes in hemoglobin levels and hematocrit were 3.5% (±2.1%) g/dL and 12.3% (±5.3%) in the THA group and 3.8% (±1.3%) g/dL and 12.0% (±3.5%) in the TKA group. There was no indication of abnormal numbers or alteration in the function of the platelets in the patients.

Discussion and Conclusions

Fondaparinux reduced asymptomatic venous thrombosis (documented by venography) by 50.6% (P<0.001) compared with enoxaparin.[6] Fondaparinux has proved to be effective in preventing most clinically relevant end points, such as post-operative mortality, pulmonary embolism, and fatal and non-fatal symptomatic venous thrombosis. Factor Xa has been shown to reduce thromboembolic complications more than other anticoagulant drugs due to greater selectivity in blocking the formation of fibrin clot by inhibiting the stabilizing role of platelet and/or blocking its amplification due to the fragments of fibrinogen formed in the venous distric. The results of the current study confirm those in the literature evaluating the efficacy of fondaparinux in preventing DVT. Fondaparinux is effective in inhibiting formation of fibrin compared to previously used drugs in thromboembolic prophylaxis, which require a double therapy with ASA or other antiplatelet drugs to prevent the thrombosis in patients with significant cardiovascular problems.

The current study evaluated the efficacy of fondaparinux for the prevention of thromboembolic events associated with post-operative DVT in patients who were receiving antiplatelet therapy. Also, in order to prevent excessive bleeding, LMWH was the pre-operative therapy and fondaparinux for 35 days post-operatively, providing the first set of data with this therapy combination.

All events were meticulously recorded because patients had regular contact with the medical team. The results demonstrated that, in selected patients with stable coronary artery disease and blood vessels, the use of fondaparinux is effective in preventing thrombotic vascular problems and reported no minor or major bleeding leading to further surgery. Patients did not present with clinical vascular thrombosis of the coronary or cerebral arteries and heart complications. Also, patients did not require a change in previous cardiac therapy. The results did not indicate any cases requiring the discontinuation of fondaparinux.

The major limitation of the current study is the lack of a comparative group. The aim of this study was to demonstrate the efficacy and safety of fondaparinux in selected patients with antiplatelet therapy in order to prevent DVT and arterial thrombotic events. The current study provided evidence for the first time on the safety and efficacy of a switch strategy prophylaxis from LMWH pre-operatively to fondaparinux post-operatively. Post-operative therapy with fondaparinux was continued avoiding the administration of antiplatelet monitoring the cardiac and cerebral function of the patients and finding an effective therapy that showed no vascular accidents related to arterial thrombosis. In addition, the single administration of fondaparinux has also reduced the risk of bleeding in the patients. In this study, there were no cases of bruising at the wound site, and abnormal bleeding was related to fondaparinux. Fondaparinux appeared to be safe and demonstrated effectiveness as a method of prophylaxis that does not involve the risks of heparin-induced thrombocytopenia. Also, the once-daily dosing regimen might be more cost-effective.[16,17]

References

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism. Chest 2008;133:381S-453S.
2. Paolucci F, Claviés MC, Necciari FDJ. Fondaparinux sodium mechanism of action: Identification of specific binding to purified and human plasma-derived proteins. Clin Pharmacokinet 2002;41:11-8.
3. Petitou M, Lormeau JC, Choay J. Chemical synthesis of glycosaminoglycans: new approaches to antithrombotic drugs. Nature 1991;350:30-3.
4. Van Boeckel CA, Petitou M. The unique antithrombin III binding domain of heparin: a lead to new synthetic antithrombotics. Angew Chem Int Ed Engl 1993;32:1671-90.
5. Oslon ST, Björk I, Sheffer R, et al. Role of the antithrombin- binding pentasaccharide in heparin acceleration of antithrombin-proteinase reactions: resolution of the antithrombin conformational change contribution to

heparin rate enhancement. J Biol Chem 1992;267: 12528-38.
6. Turpie AGG. Selective factor Xa inhibition with fondaparinux: from concept to clinical benefit. Eur Heart J Suppl 2008;10:C1-7.
7. Turpie AG, Gallus AS, Hoek JA. Pentasaccharide Investigators. A synthetic pentasac-charide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001;344:619-25.
8. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305-10.
9. Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002;359:1715-20.
10. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery:a randomised double-blind trial. Lancet 2002;359:1721-6.
11. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001;345:1298-304.
12. Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833.
13. GlaxoSmithKline. Summary of product characteristics. Arixtra® 2.5 mg and Arixtra® 1.5 mg; 2011. Available from: http://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1244136744215&featureKey=600552#nlmhighlights
14. Donat F, Duret JP, Santoni A, et al. The pharmacokinetics of fondaparinux sodium in healthy volunteers. Clin Pharmacokinet 2002;41:1-9.
15. Food and Drug Administration (FDA). Arixtra. Fondaparinux sodium. Prescription drug leaflet; 2009. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm182229.htm
16. Capri S, Ageno W, Imberti D, et al. Extended prophylaxis of venous thromboembolism with fondaparinux in patients undergoing major orthopaedic surgery in Italy: a cost-effectiveness analysis. Intern Emerg Med 2010;5:33-40.
17. Gordois A, Posnett J, Borris L, et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopaedic surgery. J Thromb Haemost 2003; 1:2167-74.