



Issue 37
August 2002

Issues in Emerging Health Technologies

Fondaparinux for Post-operative Venous Thrombosis Prophylaxis

Summary

- ✓ **Fondaparinux (Arixtra™) belongs to a new class of synthetic antithrombotic agents called pentasaccharides.¹**
- ✓ **It was recently approved in Canada for the prevention of venous thromboembolic events (VTE) in patients undergoing orthopedic surgeries of the lower limbs such as hip fracture, knee surgery and hip replacement surgery.²**
- ✓ **Fondaparinux was more efficacious in three of four phase III trials comparing fondaparinux and enoxaparin for the prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients undergoing major orthopedic surgery.³⁻⁶ However, there was no difference in the incidence of pulmonary embolism (PE) between the two treatment groups in any of the four trials.⁷**
- ✓ **The overall major bleeding rate associated with fondaparinux was higher than the rate associated with enoxaparin, although the statistical significance of this difference is inconsistent.⁸**

The Technology

Fondaparinux is a synthetic anticoagulant belonging to a new class of antithrombotic agents called pentasaccharides.¹ It is a selective, indirect inhibitor of factor Xa that interrupts the coagulation cascade by preventing the conversion of factor II (prothrombin) to factor IIa (thrombin).¹ This ultimately prevents the formation of fibrin clots.

Regulatory Status

In Canada, fondaparinux (Arixtra™) is indicated for the prophylaxis of venous thromboembolic events in patients undergoing orthopedic sur-

geries of the lower limbs such as hip fracture, knee surgery and hip replacement surgery.² It is approved for use in the US for the prophylaxis of DVT, which may lead to PE, in patients undergoing surgery for hip fracture repair, hip replacement or knee replacement.⁹ In the European Union it is approved for the prevention of VTE in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture repair, major knee surgery and hip replacement.¹⁰ It was developed by Organon and Sanofi-Synthelabo.

Patient Group

VTE includes both DVT and PE, the latter being a particularly serious complication that can lead to death.¹¹ More than 40,000 total hip and knee joint replacements were performed in Canada from 1999-2000.¹² Without anti-thrombotic prophylaxis, DVT will be diagnosed via venography in 36%-84% of patients after orthopedic surgery such as hip fracture surgery (HFS), total hip replacement (THR) and total knee replacement (TKR).¹¹ However, it is uncertain what percentage of these cases are clinically meaningful DVT events. Proximal DVT's are more likely to embolise and cause PE. The prevalence of PE is less certain and ranges from 1-30% and is fatal in 1-13% after HFS, THR and TKR.¹¹ Consequently, appropriate DVT prophylaxis is desirable.

Current Practice

The Sixth American College of Chest Physicians (ACCP) Conference on Antithrombotic Therapy recommended subcutaneous low molecular weight heparin (LMWH) or adjusted-dose warfarin in patients undergoing HFS, THR, or TKR.¹¹ Currently marketed LMWHs in Canada include dalteparin, enoxaparin, nadroparin and tinzaparin. Adjusted-dose unfractionated heparin (UFH) therapy may also be an option for THR

and HFS. Other anticoagulants such as danaparoid may be used in certain situations, such as for patients with heparin-induced thrombocytopenia. Anticoagulant prophylaxis is recommended for at least 7-10 days.¹¹ Extended out-of-hospital LMWH prophylaxis (beyond 7-10 days) may reduce the incidence of thromboembolic events and is recommended for high-risk patients.¹¹ Non-pharmacological measures such as elastic (graduated compression) stockings or intermittent pneumatic compression may also help prevent DVT.¹¹

Administration and Cost

Fondaparinux is supplied as a single dose pre-filled syringe of 2.5 mg of fondaparinux.² The recommended dose of fondaparinux is 2.5 mg subcutaneously, once daily, starting six hours after surgery, for five to nine days.² The available wholesale price of Arixtra is C\$140 for 10 pre-filled syringes of 2.5 mg fondaparinux,¹³ however, prices may vary.

Rate of Technology Diffusion

Additional information is needed to identify the role of fondaparinux in DVT prophylaxis and/or treatment. Incorporation of the drug into the ACCP guidelines for thrombosis prophylaxis may lead to a wider acceptance of the drug. Its diffusion may be affected by possible outpatient treatment via pre-filled syringes for subcutaneous injection and the fact that routine laboratory testing of prothrombin (PT) or activated partial thromboplastin time (aPTT) is not required.

In addition, future indications for fondaparinux may broaden the patient population. It has been compared to other antithrombotic agents such as dalteparin for the treatment of proximal DVT, enoxaparin for acute coronary syndrome and UHF for acute myocardial infarction.¹⁴ Ongoing trials are investigating fondaparinux compared to enoxaparin for DVT treatment and UHF for acute PE treatment.¹⁴

Acronyms used: **DVT**: deep vein thrombosis, **PE**: pulmonary embolism, **VTE**: venous thromboembolic events, **HFS**: hip fracture surgery, **THR**: total hip replacement, **TKR**: total knee replacement, **UHF**: unfractionated heparin, **LMWH**: low molecular weight heparin.

Concurrent Developments

Other investigational orthopedic surgery thromboprophylactics include nematode anticoagulant peptide c2 (NAPc2), which targets factor VIIa and tissue factor.¹⁵ It is currently in phase II trials for prophylaxis in elective knee arthroplasty. Carrier agents have been developed to improve the gastrointestinal absorption of heparin and LMWH for oral administration.^{15,16} These oral heparin compounds are in phase III trials for thromboprophylaxis in elective hip or knee arthroplasty and HFS.¹⁵ Melagatran (subcutaneous) and Ximelagatran (H376/95, oral) are thrombin inhibitors in phase III trials for thromboprophylaxis in elective hip or knee arthroplasty and treatment of venous thrombosis.¹⁵ Recombinant hirudin binds to thrombin to form a slowly reversible complex, thus inhibiting coagulation.¹⁵

The Evidence

Four phase III multicentre, randomized, double blind trials evaluating fondaparinux for the prevention of VTE were conducted in patients undergoing various major orthopedic surgeries.³⁻⁶ A dose of 2.5 mg of subcutaneous fondaparinux once daily 6±2 hours post-operatively was compared to enoxaparin 30 mg every 12 hours, starting post-operatively in North American trials [PENTAMAKS (for TKR), PENTATHLON 2000 (for THR)]. Trials outside North America studied enoxaparin 40 mg once daily, starting pre-operatively [PENTHIFRA (for HFS), EPHESUS (for THR)]. Prophylaxis was given for 7±2 days in all four studies.

The primary efficacy endpoint measured in all four trials was the incidence of VTE (defined as DVT, PE, or both) by day 11, as proven by venography of the legs between days 5 and 11, no more than two days after the last dose of the drug. Symptomatic PE was confirmed pulmonary angiography, by helical computed tomography or at autopsy. Secondary efficacy endpoints were total, proximal or distal DVT and PE (fatal and non-fatal) up to day 11 and PE (fatal and non-fatal) symptomatic VTE up to day 49.

Table 1: Summary of fondaparinux vs. enoxaparin efficacy results³⁻⁷

	Pentamaks	Pentathlon 2000	Penthifra	Ephesus
Type of Surgery	TKR	THR	HFS	THR
# Patients in efficacy analysis	724	1,584	1,250	1,827
# Patients in safety analysis	1,034	2,257	1,673	2,273
Difference ^a in VTE at day 11 [95% CI] ^b	-15.3% [-22.3; -9.3]	-2.2% [-5.5; 0.6]	-10.8% [-15.3; -6.6]	-5.2% [-8.1; -2.7]
Difference in DVT at day 11 [95% CI]	-14.6% [-21.4; -8.4]	-2.6% [-5.9; 0.2]	-10.9% [-15.4; -6.8]	-5.1% [-8.0; -2.6]
Difference in all proximal DVT at day 11 [95% CI] ^c	-3.0% [-7.6; 0.4]	0.5% [-1.0; 2.6]	-3.4% [-6.1; -1.3]	-1.8% [-3.7; -0.5]
Difference in total PE (fatal and non-fatal) at day 49 [95% CI] ^d	-0.4% [-1.7; 0.9]	0.7% [0.0; 1.5]	Same in both groups	0.1% [-0.5; 0.7]

^a Differences shown are the rates in the fondaparinux group minus the rates in the enoxaparin group

^b CI = 95% confidence interval

^c The numbers of patients with available data for this variable was higher than the efficacy population, since visualization of proximal and distal deep veins in both legs was no longer a prerequisite

^d If 95% CI values for absolute differences were unavailable, they were calculated using Confidence Interval Analysis, Version 2.0.0

Three of the four trials demonstrated superior efficacy of fondaparinux over enoxaparin for the primary efficacy endpoint, VTE ($P < 0.001$).⁷ The results from the PENTATHLON 2000 were consistent with the other trials, however, not statistically significant. In all four trials, DVT was significantly reduced by day 11. However, proximal DVT was significantly reduced ($P < 0.005$) in the PENTHIFRA and EPHEBUS trials only. There was no statistically significant difference in the incidence of PE at day 49 in any of the trials.

Adverse Effects

The primary safety outcomes measured in all four trials included fatal bleeding, bleeding in a critical organ, bleeding leading to re-operation, and overt bleeding with a bleeding index of two or more (defined as the number of units of packed red cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin values after the episode). Secondary safety outcomes were death, other bleeding and any other adverse events.

Acronyms used: **DVT**: deep vein thrombosis, **PE**: pulmonary embolism, **VTE**: venous thromboembolic events, **HFS**: hip fracture surgery, **THR**: total hip replacement, **TKR**: total knee replacement, **UFH**: unfractionated heparin, **LMWH**: low molecular weight heparin.

Table 2: Summary of fondaparinux vs. enoxaparin safety results³⁻⁸

	Pentamaks	Pentathlon 2000	Penthifra	Ephesus
Difference ^a in major bleeding at day 11 [95% CI] ^{b,c}	1.9% [0.6; 3.6]	0.8% [-0.2; 1.8]	-0.1% [-1.6; 1.4]	1.3% [-0.2; 2.8]
Difference in minor bleeding at day 11	-1.0% [-3.2; 1.2]	-0.6% [-1.8; 0.5]	2.0% [0.3; 3.7]	0.5% [-1.1; 2.1]
Difference in all cause mortality at day 49	-0.2% [-1.3; 0.9]	0.3% [-0.3; 0.9]	-0.4% [-2.5; 1.7]	-0.2% [-0.7; 0.3]
Difference in serious adverse events at day 11	1.9% [-1.1; 5.0]	0.6% [-1.1; 2.4]	0.8% [-1.6; 3.2]	0.8% [-0.8; 2.3]
Difference in withdrawals	Same in both groups	-0.4% [-2.4; 1.5]	-1.3% [-3.9; 1.2]	1.0% [-0.9; 2.9]

^a Differences shown are the rates in the fondaparinux group minus the rates in the enoxaparin group

^b CI = 95% confidence interval

^c CI values for absolute differences were calculated using Confidence Interval Analysis, Version 2.0.0

Higher major bleeding rates occurred in the fondaparinux group, although they were not statistically significant. There was no statistically significant difference for serious adverse events or adverse events between fondaparinux and enoxaparin.⁸

Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) and patients weighing < 50 kg due to possible increased risk of bleeding. Elderly patients (age > 75 years) are also at risk of bleeding.⁹

Implementation Issues

Due to the variety of effective antithrombotic agents available, such as UFH, LMWH and oral anticoagulants, it may be challenging to determine which agent should be used for specific indications.¹ It is unknown whether the cost of the drug will be a determining factor for implementation. Ultimately, the goal of prophylaxis is to prevent the morbidity and mortality associated with proximal DVT and PE. Despite four trials comparing fondaparinux to enoxaparin, it is unclear whether fondaparinux reduces the risk of clinically important VTE, and whether prophylaxis is associated with a better or worse adverse event profile compared to enoxaparin, other LMWHs or other antithrombotic strategies.

References

1. Feret B. Fondaparinux. A novel synthetic antithrombotic for prevention of venous thromboembolism. **Formulary** 2001;36:831-7.
2. ^{PR}**ARIXTRA* 2.5 mg/0.5 mL (fondaparinux sodium injection). Solution for injection: synthetic antithrombotic** [product monograph]. Toronto: Organon Sanofi-Synthelabo Canada; 2002 May 31.
3. Bauer KA, Eriksson BI, Lassen MR, Turpie AG, Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. **N Engl J Med** 2001;345(18):1305-10.
4. Eriksson BI, Bauer KA, Lassen MR, Turpie AG, Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. **N Engl J Med** 2001;345(18):1298-304.
5. Turpie AG, Bauer KA, Eriksson BI, Lassen MR, for the PENTATHLON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. **Lancet** 2002;359(9319):1721-6.
6. Lassen MR, Bauer KA, Eriksson BI, Turpie AG, for the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. **Lancet** 2002;359(9359):1715-20.
7. Lu M. Medical officer's review. NDA 21-345 (BZ, BM). Arixtra (Org31540/SR90107A, fondaparinux sodium injection) [medical review parts 5-9]. In: **Arixtra (fondaparinux sodium) injection. Company: Fonda BV. Application no.: 21-345. Approval date: 12/7/01.** Rockville (MD): Center for Drug Evaluation and Research, U.S. Food and Drug Administration; 2001. Available: http://www.fda.gov/cder/foi/nda/2001/21-345_Arixtra.htm (accessed 2002 Feb 15).
8. Farrell AT. Medical officer's safety review. NDA 21345, BM. Arixtra™ (fondaparinux sodium, Org31540/SR90107A) [medical review parts 2-5]. In: **Arixtra (fondaparinux sodium) injection. Company: Fonda BV. Application no.: 21-345. Approval date: 12/7/01.** Rockville (MD): Center for Drug Evaluation and Research, U.S. Food and Drug Administration; 2001. Available: http://www.fda.gov/cder/foi/nda/2001/21-345_Arixtra.htm (accessed 2002 Feb 15).
9. Center for Drug Evaluation and Research, Food and Drug Administration. **Arixtra (fondaparinux sodium) injection. Application number 21-345: final printed labelling.** Rockville (MD): The Center; 2001 Dec 7. Available: http://www.fda.gov/cder/foi/nda/2001/21-345_Arixtra_prntlbl.pdf (accessed 2002 Mar 15).
10. Sanofi-Synthelabo SA - France (LS:SNF) and Organon's Arixtra® (fondaparinux sodium) receives marketing authorization in the European Union. **BioSpace** [serial online] 2002 Mar 27. Available: http://www.biospace.com/news_story.cfm?StoryID=8304015&full=1 (accessed 2002 Apr 8).
11. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, Jr., et al. Prevention of venous thromboembolism. **Chest** 2001;119(1 Suppl):132S-75S.
12. Number of total hip and total knee replacement procedures performed in Canada, 1994/1995 to 1999/2000. In: **Canadian Institute for Health Information statistics a-z** [database online]: The Institute; 2002. Available: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=statistics_a_z_e (accessed 2002 Apr 8).
13. Hudson N. **[Communication to wholesalers]** [letter]. Saint-Laurent (QC): Medis Health & Pharmaceutical Services; 2002.
14. Turpie AG. Pentasaccharide Org31540/SR90107A clinical trials update: lessons for practice. **Am Heart J** 2001;142(2 Suppl):S9-S15.
15. Hirsh J. New anticoagulants. **Am Heart J** 2001;142(2 Suppl):S3-S8.
16. Conners MS, Money SR. The new heparins. **Ochsner J** 2002;4(1):41-7.

This brief was prepared by
Kirsten Garces, BSc BScPhm; CCOHTA
and has been reviewed by:

Muhammad Mamdani, PharmD MA MPH
Institute for Clinical Evaluative Sciences
Toronto, Ontario

James P. McAuley, MD FRCS
Senior Advisor, Anderson Orthopedic Research Institute
Associate Clinical Professor, University of Maryland
Alexandria, Virginia

Michael Tierney, BScPharm MSc
Director of Pharmacy, Ottawa Hospital
Ottawa, Ontario

ISSN 1488-6324 (online)
ISSN 1488-6316 (print)
Publications Agreement Number 40026386