National PBM Drug Monograph

Fondaparinux sodium (Arixtra®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Introduction

Patients who do not receive thromboprophylaxis after an orthopedic surgery procedure will likely develop a deep venous thrombosis (DVT). The incidence of this complication is variable based on the type of procedure. In the absence of prophylaxis, as many as 86% of patients undergoing knee replacement will develop a DVT in the first day post- surgery. The incidence is somewhat lower with hip replacement; a 50% likelihood in the absence of thromboprophylaxis. Those with hip surgery experience an increased risk for up to 3 weeks after surgery. The risk of DVT stabilizes after 4 weeks in knee replacement and 10 weeks in hip replacement. Current commonly used agents for thromboembolism prophylaxis include unfractionated heparin (UFH) and low molecular weight heparin (LMWH).

Pharmacology/Pharmacokinetics

The site of action for fondaparinux is antithrombin III (ATIII) where the agent selectively binds and potentiates the neutralization of Factor Xa by ATIII. This results in a disruption of the coagulation cascade, inhibiting thrombus formation.

Fondaparinux is administered by subcutaneous injection with rapid and complete absorption. In patients receiving treatment, C_{max} is achieved approximately 3 hours post dose. The drug is distributed in blood with only a small proportion going to the extravascular fluid. Steady state volume of distribution is 7-11L. Since fondaparinux is specific in binding to ATIII, there is negligible binding to plasma proteins or red blood cells. The elimination half-life for the drug is 17-21 hours. The primary route of elimination is urinary excretion of unchanged drug.

FDA Approved Indication(s) and Off-label Uses

Fondaparinux is indicated for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing hip facture surgery, hip replacement surgery and knee replacement surgery. Prevention of DVT may prevent development of pulmonary embolism in these patients. The FDA approved the agent in 2001 with a 1-P rating.

Dosage and Administration

The recommended dose of fondaparinux is 2.5 mg given by subcutaneous injection once daily. The initial dose of medication is administered after postsurgical hemostasis is established, usually 6 to 8 hours after surgery. The medication is supplied as a prefilled injector, with explicit instructions for use.

Adverse Effects (Safety Data)

The most common adverse effects with fondaparinux treatment are bleeding complications. In knee replacement surgery, major bleeding, defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g., intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation at operative site,

or (4) with a bleeding index (BI) ≥2. BI ≥2: overt bleeding associated only with a bleeding index (BI) ≥2 [calculated as number of whole blood or packed red blood cells transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values was significantly greater in patients receiving fondaparinux than enoxaparin sodium-treated patients, 2.1% versus 0.2% respectively.

The rates of bleeding, both major and minor are described in Table 1.

Table 1. Bleeding across Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies

Indications	Fondaparinux Sodium 2.5 mg SC once daily	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium[1]
	N = 3616	N = 3956
Major Bleeding	96 (2.7%)	75 (1.9%)
Fatal Bleeding	0 (0.0%)	1 (<0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (<0.1%)
Re-operation due to bleeding	12 (0.3%)	10 (0.3%)
(BI) ≥2	84 (2.3%)	63 (1.6%)
Minor Bleeding[4]	109 (3.0%)	116 (2.9%)

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Other

Other adverse events that occurred during clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery and that occurred at a rate of at least 2% in either treatment group, are provided in Table 2 below.

Table 2. Adverse Events Occurring in ≥2% of ARIXTRA or Enoxaparin Sodium Treated Patients Regardless of Relationship to Study Drug Across Hip Fracture Surgery, Hip Replacement Surgery, or Knee Replacement Surgery Studies

Adverse events	Fondaparinux Sodium 2.5 mg SC once daily N = 3616	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium[1] N = 3956
Anemia	707 (19.6%)	670 (16.9%)
Fever	491 (13.6%)	610 (15.4%)
Nausea	409 (11.3%)	484 (12.2%)
Edema	313 (8.7%)	348 (8.8%)
Constipation	309 (8.5%)	416 (10.5%)
Rash	273 (7.5%)	329 (8.3%)
Vomiting	212 (5.9%)	236 (6.0%)
Insomnia	179 (5.0%)	214 (5.4%)
Wound drainage increased	161 (4.5%)	184 (4.7%)
Hypokalemia	152 (4.2%)	164 (4.1%)

Urinary tract infection	136 (3.8%)	135 (3.4%)
Dizziness	131 (3.6%)	165 (4.2%)
Purpura	128 (3.5%)	137 (3.5%)
Hypotension	126 (3.5%)	125 (3.2%)
Confusion	113 (3.1%)	132 (3.3%)
Bullous eruption	112 (3.1%)	102 (2.6%)
Urinary retention	106 (2.9%)	117 (3.0%)
Hematoma	103 (2.8%)	109 (2.8%)
Diarrhea	90 (2.5%)	102 (2.6%)
Dyspepsia	87 (2.4%)	102 (2.6%)
Post-operative hemorrhage	85 (2.4%)	69 (1.7%)
Headache	72 (2.0%)	97 (2.5%)
Pain	62 (1.7%)	101 (2.6%)

[1] Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

Precautions/Contraindications

Fondaparinux is contraindicated in patients with severely impaired kidney function or in patients who weigh less than 110 pounds, because they may have an increased risk for major bleeding. Patients greater than 75 years of age also may be more likely to experience major bleeding due to a 25% lower clearance of the agent. As with other antithrombotics, labeling for fondaparinux includes a boxed warning regarding use when spinal anesthesia or spinal puncture is used because of possible spinal/epidural hematomas.

Drug Interactions

The concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin has not been shown to significantly alter the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, were not altered.

In an *in vitro* study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 µM i.e., 350 mg/L) was 17-28%. Inhibition of the other isozymes evaluated (CYPs 2A1, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0-16%. Since fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*, fondaparinux sodium is not expected to significantly interact with other drugs *in vivo* by inhibition of metabolism mediated by these isozymes.

Since fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, no drug interactions by protein-binding displacement are expected.

Clinical Trials

Citation	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.
Study Goals	To determine the efficacy of fondaparinux in thromboprophylaxis after hip fracture surgery.
Methods	• **Study Design** ➢ Multicenter, randomized, double blind ➢ N=1711 across 99 centers and 21 countries (no United States sites) ➢ Day 1 was day of surgery, treatment continued for 5-9 days ➢ Primary outcome, assessed at day 5-11 ➢ Followup between day 35-49 ➢ Primary outcome-incidence of venous thromboembolism up to day 11 ➢ Bilateral venography was mandatory ➢ Fondaparinux 2.5 mg SQ daily, enoxaparin 40 mg SQ daily • **Data Analysis** ➢ A 22% incidence of VTE by day 11 was assumed ➢ A risk reduction of 30% was anticipated, power was 85%
Criteria	• **Inclusion criteria** ➢ At least 18 years of age ➢ Standard surgery for fracture of the upper third of the femur within 48 hours of admission • **Exclusion criteria** ➢ Serum creatinine > 2 mg/dl ➢ Platelet count < 100,000/mm^3 ➢ multiple trauma ➢ greater than 24 hours between injury and hospital admission ➢ pregnancy ➢ active bleeding ➢ history of congenital or acquired bleeding disorder ➢ history of hemorrhagic stroke or brain, spinal, ophthalmologic surgery in previous 3 months ➢ planned use of indwelling epidural catheter
Results	

Efficacy Measure	Fondaparinux	Enoxaparin	ARR	NNT	95%CI	p
Incidence of VTE by day 11	52/626(8.3%)	119/624(19.1%)	10.8%	10	15.3-6.6%	<0.001
Treated by physician for VTE by day 11	43/702(6.1%)	84/716(11.7%)	5.6%	20		<0.001
Any deep vein thrombosis	49/624(7.9%)	117/623(18.8%)	10.9%	10	15.4-6.8%	<0.001
Symptomatic VTE	4/831(0.5%)	4/840(0.5%)				1.00

Safety Outcome	Fondaparinux (N=831)	Enoxaparin (N=842)	p
Major bleed	18	19	1.00
Minor bleed	34	18	0.02
Mean number units transfused	2.7± 1.5	2.8± 1.8	
Death from any cause	11	16	

Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g., intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥2. BI ≥2: overt bleeding associated only with a bleeding index (BI) ≥2 [calculated as number of whole blood or packed red blood cells transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].

Conclusions	Fondaparinux was more effective than enoxaparin 40 mg daily in preventing venous thromboembolism. The agents were equally safe, with no significant differences in major and minor bleeding.
Critique	• **Strengths** • Defined outcome measure followed with bilateral venography • Large study size with multiple centers and investigators • Use of bleeding index to account for patients with lower hemoglobin levels prior to study • **Limitations** • A steering committee composed of 10 people (6 representatives from the pharmaceutical sponsor) designed, interpreted and authored the manuscript of the trial. • No US centers in trial • No clear definition of when treatment was to end • No set protocol to treat VTE • Duration of treatment may have been too short for high risk patients • Low incidence of pulmonary embolism may have been influenced by early venography

Citation	Bauer KA ,Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305-10.
Study Goals	To determine the efficacy of fondaparinux in thromboprophylaxis after knee surgery.
Methods	• **Study Design** ➢ Multicenter, randomized, double blind ➢ N=1049 across 64 centers in North America ➢ Day 1 was day of surgery, treatment continued for 5-9 days ➢ Primary outcome, assessed at day 5-11 ➢ Followup between day 35-49 ➢ Primary outcome-incidence of venous thromboembolism up to day 11 ➢ Bilateral venography was mandatory ➢ Fondaparinux 2.5 mg SQ daily, enoxaparin 30 mg SQ twice daily • **Data Analysis** ➢ Incidence of VTE assumed to be 34%, anticipated risk reduction 30% ➢ Power 85%
Criteria	• **Inclusion criteria** ➢ At least 18 years of age ➢ Elective major knee surgery defined as resection of the distal end of the femur or proximal end of the tibia or a revision of at least one component of previously implanted total knee prosthesis. • **Exclusion criteria** ➢ Serum creatinine > 2 mg/dl ➢ Platelet count < 100,000/mm^3 ➢ multiple trauma ➢ greater than 24 hours between injury and hospital admission ➢ pregnancy ➢ active bleeding ➢ history of congenital or acquired bleeding disorder ➢ history of hemorrhagic stroke or brain, spinal, ophthalmologic surgery in previous 3 months ➢ planned use of indwelling epidural catheter ➢ surgery in contralateral knee was simultaneous or planned within 2 weeks

Results

Efficacy Measure	Fondaparinux	Enoxaparin	ARR	NNT	95%CI	p
Incidence of VTE by day 11	45/361(12.5%)	101/363(27.8%)	15.3 %	6	22.3-9.3%	<0.001
Any deep vein thrombosis	45/361(12.5%)	98/361(27.1%)	14.6 %	7	21.4-8.4%	<0.001
Symptomatic VTE	3/517(0.6%)	7/5171.4%)	0.8%		-3.3-1.1%	0.34

Safety Outcome	Fondaparinux (N=517)	Enoxaparin (N=517)	p
Major bleed	11	1	0.006
Minor bleed	14	19	
Mean number units transfused	1.9±1.1	1.8±0.9	
Death from any cause	1	2	

Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g., intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥2. BI ≥2: overt bleeding associated only with a bleeding index (BI) ≥2 [calculated as number of whole blood or packed red blood cells transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].

Conclusions

Treatment with fondaparinux was more effective than treatment with enoxaparin for VTE prophylaxis in elective major knee surgery. There was no difference in the prevention of proximal DVT in the two treatment groups. The incidence of major bleeding was significantly more with fondaparinux treatment.

Critique

- **Strengths**
- Defined outcome measure followed with bilateral venography
- Large study size with multiple centers and investigators
- Use of bleeding index to account for patients with lower hemoglobin levels prior to study
- **Limitations**
- A steering committee composed of 10 people (7 representatives from the pharmaceutical sponsor) designed, interpreted and authored the manuscript of the trial.
- No clear definition of when treatment was to end
- No set protocol to treat VTE
- Duration of treatment may have been too short for high risk patients

Low incidence of pulmonary embolism may have been influenced by early venography

Acquisition Costs

Elective major knee surgery

Drug	Dose	Cost/Day/patient ($)
Fondaparinux	2.5 mg QD	26.05
Enoxaparin	30 mg BID	18.52

Hip Fracture repair surgery

Drug	Dose	Cost/Day/patient ($)
Fondaparinux	2.5 mg QD	26.05
Enoxaparin	40 mg QD	12.85

Conclusions

The mechanism of action for fondaparinux provides a unique method of inhibiting the coagulation pathway. Given the specific binding of this agent it may provide benefit over currently available agents. The clinical trials conducted with this agent have shown superiority to the doses of enoxaparin used. However, fondaparinux showed a significant increase in the episodes of major bleeding in the knee surgery trial.

There are concerns regarding the use of fondaparinux in elderly patients and in those with decreased renal function. The drug interaction profile of the agent appears minimal with commonly employed agents.

Once daily dosing of fondaparinux offers advantages, as does the use of a prefilled syringe.

Recommendations

Fondaparinux sodium should remain non-formulary. Presently the only information available is in knee and hip surgery with trials in unstable angina, treatment of DVT/PE and trauma/surgery prophylaxis of VTE underway. There is a significant cost difference between fondaparinux and enoxaparin. Additionally, the concern of using this agent in patients over 75 years and with compromised renal function may impact a large proportion of VA patients. Fondaparinux would remain an option for patients with allergy to LMWH products.

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