**Educational Objectives**

- Compare fondaparinux’s mechanism to that of low-molecular-weight heparins (LMWHs)
- Explore the efficacy and safety of fondaparinux use
- Review the recommended dose and administration of fondaparinux

**Fondaparinux: The First Pentasaccharide Anticoagulant**

Nicole T. Ansani, PharmD

Despite advances in anticoagulation therapy, venous thromboembolism (VTE) remains a major clinical concern. The incidence and risk of VTE following major orthopedic surgeries is well documented. In addition, because of the clinically silent nature of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the associated morbidity and mortality, a clear rationale for VTE prophylaxis following orthopedic surgeries has been demonstrated.

Fondaparinux is the first in a new class of pentasaccharide anticoagulant agents, and is FDA-approved for use in the prophylaxis of DVT that could lead to PE in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery.

**Pharmacology/Pharmacodynamics**

Traditional anticoagulants, such as unfractionated heparin (UFH), exert efficacy via inhibition of the extrinsic clotting factors Xa and IIa. As a result of enzymatic cleavage, low-molecular-weight heparins (LMWHs) are smaller heparin fragments (approximately one third of the size of UFH), and they show an increased propensity for the inhibition of factor Xa compared to IIa activity. In both circumstances, the UFH/LMWH agents are associated with bleeding complications, biological variability, pathogenic contamination, and cross-reactivity with heparin-platelet factor 4 antibody, which can cause heparin-induced thrombocytopenia and thrombosis (HITT). Fondaparinux is a purely synthetically derived pentasaccharide agent. It differs from UFH and LMWH, which are extracted from animal sources.

In addition, in contrast to UFH and LMWHs, fondaparinux exerts its anticoagulant effect solely via antithrombin-III mediated neutralization of factor Xa and is devoid of IIa inhibition. Specifically, fondaparinux selectively binds to antithrombin III, leading to a conformational shift that leads to a thousand-fold increase in factor Xa inhibition via antithrombin. Fondaparinux binds to antithrombin by a 1:1 ratio and thus results in a permanent conformational shift in antithrombin after the Xa complex is formed. However, fondaparinux does not bind to platelet factor 4 and therefore does not affect platelet function or platelet aggregation, thereby lending to the need to further evaluate use in patients with HITT.

The molecular size of fondaparinux is 1.7kD, compared to approximately 4 to 6kD with LMWHs and 15kD with UFH, lending to potentially greater specificity and improved biological properties.

Potential advantages of this agent, based on the pharmacodynamic profile and purely synthetic nature include: minimization/elimination of biological variability, immunogenic reactivity, and pathogenic contamination.

**Pharmacokinetics**

Single- and multiple-dose pharmacokinetic evaluations were performed in three phase I studies involving healthy volunteers. Doses of fondaparinux utilized ranged from 0.36 to 28.6 mg. Results of this evaluation showed that doses less than 1.4 mg did not produce measurable plasma anti-Xa activities. However, doses above 1.4 mg showed a proportionate increase in anti-Xa activity (results reported in this section reflect doses greater than 1.4 mg). A maximum concentration ($C_{max}$) was achieved within 1.9 ± 0.8 hours after single-dose administration. The half-life of fondaparinux was 13.3 ± 3.3 hours, irrespective of dose. There was a linear dose relationship seen with elimination; 24 hours following the first dose administration, 37% to 70% of fondaparinux was recovered in the urine. When evaluating the clearance in elderly patients and/or patients with decreased renal function, significant increases in half-life ($P<0.001$) and decreases in clearance ($P<0.001$) were seen. Following multiple-dose evaluations, steady state was achieved within two to three days. However, no significant changes in pharmacokinetic parameters compared to the single-dose studies were noted.
Weighing less than 45 to 50 kg. In general, these agents should not be used in patients with a creatinine clearance below 30 mL/minute. In addition, dalteparin, enoxaparin, and fondaparinux all exhibit linear dose-related activity. Caution must be used in patients weighing less than 45 to 50 kg.

Clinical Trials

Clinical trials have primarily focused on the efficacy and safety of fondaparinux compared to LMWH for VTE prophylaxis. To date, four large phase III trials are only available in select orthopedic procedures. Phase II studies have been performed to evaluate the efficacy and safety of fondaparinux in VTE treatment and acute coronary syndrome (ACS), phase III trials are currently ongoing in these areas.

DVT Prophylaxis

Turpie et al. evaluated the efficacy and safety of fondaparinux compared to LMWH in patients undergoing total hip replacement surgery. Patients were randomized to therapy with fondaparinux 0.75, 1.5, 3, or 8 mg subcutaneously (SC) six hours post-operatively, then once daily; or enoxaparin 30 mg every 12 hours, SC 12 hours to 24 hours post-operatively, then every 12 hours daily. Therapy was continued for five to 10 days. The primary efficacy endpoint was incidence of VTE. Clinically suspected VTE necessitated confirmation by venography or lung scan. Major and minor bleeding was also assessed.

No significant differences in baseline demographics were noted. Patients ranged in weight from 45 to 135 kg. Enrollment in to the fondaparinux 8- and 6-mg arms was stopped after 52 and 72 patients, respectively, because of a high incidence of major bleeding (11.5% and 12.5%, respectively). In addition, three bleeds were seen in each of these arms after the cessation of study protocol. The incidence of VTE was associated with a dose-related effect of fondaparinux. VTE was experienced in 11.8%, 6.7%, and 1.7% of patients in the 0.75-, 1.5-, and 3-mg groups, respectively, compared to 9.4% in the enoxaparin group. The incidence of VTE was significantly decreased in the 3-mg group compared to the 0.75-mg, 1.5-mg, and enoxaparin groups (P=0.003, P=0.01, and P=0.01, respectively). The observed VTE risk reduction was significantly reduced (82% risk reduction) in the 3-mg fondaparinux group compared to enoxaparin (P=0.01).

Major bleeding occurred in a similar percentage of patients with fondaparinux 3 mg and enoxaparin. However, significant decreases in bleeding were seen with fondaparinux 0.75 or 1.5 mg compared to enoxaparin (P=0.01 and P=0.05, respectively). No deaths or HIT were seen during the treatment period.

Lassen et al. reported the results of a multicenter study evaluating fondaparinux compared to enoxaparin in patients undergoing hip replacement surgery (EPHESUS). Patients were randomized to receive fondaparinux 2.5 mg SC daily (started six to 12 hours post-operatively) or enoxaparin 40 mg SC daily, started 12 hours pre-operatively, followed by a second dose 12 to 24 hours post-operatively, and then daily thereafter. Therapy was continued for five to nine days. The primary analysis evaluated was incidence of VTE on day 11.

The primary safety endpoint was major bleeding. Secondary endpoints included: total, proximal, or distal DVT, or symptomatic VTE up to day eleven, and symptomatic VTE up to day 49. The primary safety endpoint was major bleeding. Secondary safety endpoints included: death, minor bleeding, incidence of adverse drug events, and platelet count.

Baseline demographics were similar between the groups. Doses of enoxaparin were administered preoperatively in 78% of patients; the remaining 22% received enoxaparin post-operatively, primarily because of regional anesthesia. At day eleven, there was a significant reduction in the incidence of VTE with fondaparinux (4%) compared to enoxaparin (9%), lending to a relative risk reduction of 55.9% (P=0.001). In addition, the incidence of any DVT, proximal DVT, or distal DVT was significantly reduced with fondaparinux (4%, 1%, and 3%, respectively) compared to enoxaparin (9%, 2%, and 7%, respectively); relative risk reduction of 56.1% (P=0.001), 73.8% (P=0.002), and 54.8% (P=0.001). No difference in symptomatic VTE was seen between the groups. At day 49, there was no difference in the percentage of patients experiencing symptomatic VTE between groups (1% for each). No difference was noted in
Pharmacokinetic Parameters of Fondaparinux and Other Anticoagulants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fondaparinux</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Lepirudin</th>
<th>Argatroban</th>
<th>Danaparoid</th>
<th>UFH</th>
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<tr>
<td>Bioavailability</td>
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<td>92%</td>
<td>87%</td>
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<tr>
<td>Half-life</td>
<td>13 hours</td>
<td>4 hours</td>
<td>3 hours</td>
<td>1.3 hours</td>
<td>0.5 hours</td>
<td>Factor Xα = 24.5 hours</td>
<td>Factor IIa = 4.3 hours</td>
</tr>
</tbody>
</table>

*Note this is a comparison of published data and not a direct comparison via a pharmacokinetic evaluation of all agents.*

major bleeds. In addition, no differences in other bleeds, death, adverse events, transfusion requirements, platelet count, or incidence of HIT were seen between the groups.

Another study evaluated the efficacy and safety of fondaparinux compared to enoxaparin in patients undergoing hip replacement surgery (PENTATHLON 2000). Patients were randomized to receive fondaparinux 2.5 mg SC daily, started four to eight hours post-operatively, or enoxaparin 30 mg every 12 hours started post-operatively (time not specified). Therapy was continued for five to nine days. The primary analysis was incidence of VTE at day 11 and safety analysis was major bleeding. Secondary endpoints were identical to the EPHESUS study.

Baseline demographics were similar between the groups. Results of this study show that there was no difference in the incidence of VTE at day eleven with fondaparinux (6%) compared to enoxaparin (8%), relative risk reduction, 26.3% (P=0.099). In addition, there were no differences in proximal DVT between groups (P=0.42). However, a significant decrease in the incidence of DVT and distal DVT was seen with fondaparinux (6% and 4%) compared to enoxaparin (8% and 7%), lending to a relative risk reduction of 31.3% (P=0.047) and 36.7% (P=0.037), respectively. Significantly fewer symptomatic VTEs were seen with enoxaparin (0.1%) compared to fondaparinux (1%), P=0.0062. At day 49, significantly fewer enoxaparin patients experienced symptoms of VTE (1%) compared to fondaparinux (3%), P=0.013. Eleven fondaparinux patients (1%) and two enoxaparin patients (0.1%) experienced non-fatal PEs (P not reported). No difference in major bleeding was seen between the groups. In addition, no differences in other secondary endpoints were noted.

The efficacy and safety of fondaparinux compared to enoxaparin following hip fracture surgery was compared by Eriksson et al. Patients were randomized to therapy with fondaparinux 2.5 mg SC started six hours post-operatively, then daily (at least 12 hours after the first dose), or enoxaparin 40 mg SC started 12 hours pre-operatively, then a second dose 12 to 24 hours post-operatively, then daily thereafter. Both agents were continued for five to nine days. The primary efficacy endpoint was incidence of VTE at day 11. Secondary efficacy endpoints included total, proximal, or distal DVT, or symptoms of VTE up to day 11 and symptomatic VTE up to day 49. The primary safety endpoint was major bleeding. Secondary safety endpoints were death and minor bleeding.

Baseline characteristics and reasons for exclusion from analysis were similar between the groups. Doses of fondaparinux were administered pre-operatively to 10.9% of patients because of delayed surgery. In the enoxaparin group, 74.4% of patients were initiated on therapy post-operatively because of early surgery or planned regional anesthesia. At day 11, there was a significant decrease in the incidence of VTE between fondaparinux (8.3%) and enoxaparin (19.1%), (P=0.001). The reported difference showed a 56.4% relative risk reduction in VTE. The secondary endpoints of total, proximal, and distal-only DVT were also significantly reduced with fondaparinux (7.9%, 0.9%, and 6.7%, respectively) compared to enoxaparin (18.8%, 4.3%, and 15%, respectively) (P<0.001 for all three endpoints). No differences in symptomatic VTE were noted between groups during the initial follow-up period. At day 49, no difference in symptomatic VTE was seen between groups. No difference in PE or fatal PE was seen between groups. No differences in major bleeding were reported. However, a significant increase in minor bleeding was seen with fondaparinux compared to enoxaparin (P=0.02). No differences were exhibited in death, wound infection, or HITT.

Bauer et al. compared the efficacy and safety of fondaparinux versus enoxaparin in patients undergoing major knee replacement surgery. Patients were randomized to receive fondaparinux 2.5 mg SC, which started six hours post-operatively—the second dose was given at least 12 hours later, then daily thereafter—or enoxaparin 30 mg SC, started 12 to 24 hours post-operatively, then every 12 hours thereafter. Therapy was continued for five to nine days. The primary efficacy outcome evaluated was the rate of VTE at 11 days. Secondary efficacy endpoints included total, proximal, or distal VTE, and symptoms of VTE up to day 49. The primary safety outcome was major bleeding. Secondary safety outcomes included death, HITT, other bleeding, the need for transfusion, or other adverse drug events (ADEs).
No differences in baseline characteristics or reasons for exclusion from study were seen between the groups. Results revealed a significant decrease in the incidence of VTE at day 11 with fondaparinux (12.5%) compared to enoxaparin (27.8%), lending to a relative risk reduction of 55.2% (P<0.001). No differences in proximal DVT or the number of symptomatic VTEs were seen between groups. Fondaparinux was associated with a significantly lower incidence of proximal DVT (2.4%) compared to enoxaparin (5.24%), relative risk reduction, 54.5% (P<0.001).

In addition, the number of patients treated for VTE at day 11 was significantly lower with fondaparinux than with enoxaparin (P<0.001). At day 49, no differences in the incidence of VTE, fatal PE, or PE were noted between the groups. A significant increase in major bleeding was seen between fondaparinux (2.1%) compared to enoxaparin (0.2%) (P=0.006). However, no differences in minor bleeding, the need for transfusion, platelet count, or other ADEs were seen between the groups.

The impact of the differences in dosing schedules for these agents is unknown. It has been proposed that the administration of early antithrombotic prophylaxis post-operatively might be more effective than delayed therapy. However, currently, there are no DVT prophylaxis studies with fondaparinux administered at the same time as the LMWH. Further, the dosing schedules utilized for enoxaparin include the literature-supported, and FDA- and manufacturer-recommended administration schedules.

A recent publication reports the pooled estimated incidence of VTE, proximal DVT, and major bleeding from the four phase III trials. Results show that there is a decrease in the incidence of VTE with fondaparinux (6.8%) compared to enoxaparin (13.7%); however, this finding is not statistically significant (P=0.0581). A significant decrease in proximal DVT was noted; 1.3% for fondaparinux compared to 2.9% with enoxaparin (P=0.00542). No difference in major bleeding was reported in the pooled data estimate (P=0.0583).

VTE Treatment

The REMBRANDT investigators evaluated the efficacy and safety of fondaparinux compared to dalteparin in the treatment of VTE in a randomized, parallel group, dose-ranging study. Four-hundred and fifty-three patients were randomized to therapy with fondaparinux 5, 7.5, or 10 mg SC daily or 100 u/kg dalteparin SC twice daily. Vitamin K antagonist therapy began on days one or two and continued for at least 90 days. Doses were adjusted to a goal international normalized ratio (INR) of 2 to 3. The study drug was discontinued after two consecutive therapeutic INRs, or at least five days of therapy. The primary endpoint evaluated was a change in thrombus mass in the affected limb(s). Clinical outcome assessment included patient reports of symptomatic VTE and bleeding.

In the intent-to-treat arm (n=438), 45.2% of fondaparinux patients and 48.7% of dalteparin patients had a positive outcome, confidence interval (CI) -7.2% to 15%. Results were similar when evaluating the per protocol cohort (n=289), (CI = -10.8% to 12.4%). Symptomatic and current VTE rates were similar between groups, 2.4% for fondaparinux compared to 5% for dalteparin (CI = -2.1%–10.1%). No differences in major bleeding, any bleeding, or death were noted between the groups.

Phase III trials are necessary to determine the optimal place in therapy for fondaparinux in VTE treatment.

Acute Coronary Syndrome

The Pentalyse study evaluated the comparative efficacy and safety of fondaparinux and UFH as an adjunct to alteplase in patients with ST-segment elevation acute myocardial infarction (AMI) in a randomized, open-label parallel group, dose-ranging, multicenter trial. Three hundred and twenty-six patients received therapy with fondaparinux 6, 8, or 12 mg IV once dose, then SC daily for five to seven days; or UFH IV 5000 units bolus, then 1000 unit/hr for 48 to 72 hours (adjusted to aPTT of 50–75 seconds). All patients received front-loaded alteplase over 90 minutes and 150 to 325 mg of aspirin daily. The primary outcomes included TIMI flow grades at 90 minutes and days five and seven, and intracranial hemorrhage or other bleeding requiring blood transfusion. Secondary endpoints included other bleeding. No differences in TIMI grade 3 flow rate, death, reinfarction, or revascularization were seen between the groups (P not reported). In addition, no differences in major or minor bleeding were reported between the groups.

Larger trials evaluating fondaparinux in ACS are necessary to determine its place in therapy for this indication. Data from the PENTUA trial were presented at the fall 2001 American Heart Association Meeting. This study evaluated fondaparinux compared to enoxaparin in more than 1,000 patients. Results reported that fondaparinux is at least as safe and effective as enoxaparin for ACS; further investigations are needed.

Adverse Drug Events

Bleeding is the most common ADE associated with fondaparinux use. In the clinical trial evaluating fondaparinux for DVT prophylaxis in knee replacement surgery, Bauer et al. found a significantly increased risk of major bleeding with fondaparinux (2.17%) compared to enoxaparin (0.2%), (P=0.006). However, other similar studies (in hip fracture and hip replacement surgery) have not shown an increased risk of major bleeding compared to enoxaparin (see Table 2).

Aggregate data reports the incidence of major bleeding in 3,616 fondaparinux patients and 3,956 LMWH patients as 2.7% and 1.9%, respectively. Minor bleeding has been reported in 3% of fondaparinux patients and 2.9% of LMWH patients.

Other ADEs experienced in clinical trials included mild local irritation and asymptomatic increases in AST and ALT. ADEs occurring in greater than 5% of patients studied include: anemia, fever, nausea, edema, constipation, rash, vomiting, and insomnia.
The incidence of HIT associated with fondaparinux might be theoretically nonexistent because the drug lacks platelet factor-4 binding. In vitro studies evaluating the cross-reactivity of enoxaparin, danaparoid, and fondaparinux with the HIT antibody showed positive tests in 76%, 8%, and 0% of samples, respectively.4

**Dose/Administration**

The manufacturer- and FDA-recommended dose of fondaparinux is 2.5 mg SC daily. This agent should be initiated six to eight hours post-operatively (use before this period has reportedly been associated with an increased risk of bleeding).3 The usual duration of use is five to nine days; use up to 11 days has been shown to be safe and effective.3 Increased concentrations of fondaparinux and a decreased half-life have been seen with the elderly and in patients with renal insufficiency.3 No formal dose reduction recommendations, however, are available. Fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/minute) and in patients weighing less than 50 kg because of the potential for increased bleeding.3

**Cost**

Fondaparinux is more costly than existing LMWHs; however, formal pharmacoeconomic analyses are not available. The Actual Wholesale Price (AWP) of fondaparinux 2.5 mg daily is $43.50, whereas enoxaparin 30 mg every 12 hours or 40 mg daily is $36.70 and $24.46, respectively, and dalteparin 5,000 units daily is $24.90.30-31

**Place in Therapy**

Fondaparinux has shown consistent benefit with little increased risk of bleeding over other LMWHs in clinical trials for VTE prophylaxis.19-23 Because of its small size, specific binding to Xa, and high bioavailability, potential advantages over UFH and LMWHs, such as decreased biological variability, decreased pathogenic contamination, and decreased propensity for HIT, can be seen. Use in VTE prophylaxis with fondaparinux, however, has only been evaluated following selected orthopedic procedures.19-23 In addition, differences in timing and the initiation of anticoagulation have been seen in these studies. Small dose-ranging studies have com-
pared fondaparinux to UFH or LMWH for ACS and VTE treatment, respectively. However, at this time, there is not sufficient data to support its use outside of prophylaxis following knee and hip replacement surgery or hip fracture surgery. In these indications, fondaparinux might be an alternative agent to LMWHs. According to the Chest 2001 Guidelines1 (published prior to fondaparinux approval), a level of evidence score “1A” (randomized trials without limitations) was given to support the use of LMWHs in elective knee and hip replacement surgery.

With regard to hip fracture surgery, the level of evidence supporting LMWH is graded as “1B” (randomized trials with important limitations). The use of fondaparinux in this population (hip fracture surgery patients) might be particularly attractive because of the published results and significant findings of the Eriksson study.22 In knee replacement surgery, fondaparinux is associated with increased efficacy at the risk of decreased safety compared to enoxaparin. Phase III data supporting the use of fondaparinux in hip replacement surgery shows a lower incidence of VTE compared to enoxaparin; however, these findings were only significant when compared to enoxaparin 40 mg orally daily (EPHESUS trial). The use of fondaparinux in patients with a history of HITT needs to be further evaluated.

Although LMWHs are associated with a lower incidence of HITT than UFH, cross-reactivity of the HITT antibody is likely to be seen with LMWHs.15 Clinical trials with fondaparinux to date have all excluded patients with a history of heparin allergy and/or low baseline platelet count. However, in vitro studies have not shown cross-reactivity with the HITT antibody. Fondaparinux is not recommended for patients with severe renal insufficiency or in patients weighing less than 50 kg.3 This agent is more costly than the LMWHs approved for VTE prophylaxis in the U.S.30-31 Fondaparinux appears to be a novel alternative for VTE prophylaxis following orthopedic surgeries. However, use outside of these indications cannot be supported at this time.

References


Disclosure

Dr. Ansani has declared that she received an honorarium from Organon Sanofi-Synthelabo, LLC for attending the Synergy Medical Education Conference held April 26-28, 2002, after this article was written.
1. The activity of fondaparinux includes all of the following, except
   a. antithrombin III selective binding.
   b. factor Xa inhibition.
   c. platelet factor-4 binding.
   d. factor IIa inhibition.

2. Which of the following is incorrect regarding the pharmacokinetic profile of fondaparinux?
   a. Cmax within 1.9 ± 0.8 hours
   b. T1/2 of 13.3 ± 3.3 hours
   c. The liver is the primary route of elimination
   d. Steady state is achieved in two to three days

3. Which statement regarding studies of fondaparinux for DVT prophylaxis is incorrect?
   a. The studied population includes total hip replacement surgery patients.
   b. The majority of the studies compare fondaparinux with enoxaparin.
   c. A dose–response effect was not seen.
   d. No deaths have been reported because of HITT.

4. Clinical trials have evaluated the efficacy and safety of fondaparinux for the prophylaxis of DVT under which of the following conditions?
   a. hip fracture surgery
   b. hip replacement surgery
   c. knee replacement surgery
   d. all of the above

5. Fondaparinux is administered
   a. orally and subcutaneously (SC).
   b. as an intravenous (IV) bolus.
   c. subcutaneously.
   d. SC and as an IV bolus.

6. The most common side effect of fondaparinux is
   a. headache.
   b. bleeding.
   c. blurry vision.
   d. dizziness.

7. Which of the following statements is incorrect?
   a. Eriksson et al. reported a 56.4% relative risk reduction in VTE associated with the use of fondaparinux.
   b. The Pentalyse study evaluated the comparative efficacy and safety of fondaparinux and UFH as an adjunct to alteplase.
   c. Bauer et al. reported a 55.2% relative risk reduction in VTE associated with the use of fondaparinux.
   d. It has been proposed that late administration of antithrombotic prophylaxis post-operatively might be more effective than early therapy.

8. Which of the following statements is correct about fondaparinux usage?
   a. Fondaparinux should be initiated 12 hours post-operatively.
   b. The duration of therapy is two to three days.
   c. The FDA-recommended dose is 2.5 mg SC daily.
   d. The FDA-recommended dose is 15 mg SC daily.

9. Which of the following statements is correct about the cost of fondaparinux?
   a. Fondaparinux is less expensive than enoxaparin.
   b. Fondaparinux is more expensive than enoxaparin.
   c. Multiple pharmacoeconomic studies have been conducted on fondaparinux.
   d. None of the above.

10. Which of the following statements about fondaparinux is incorrect?
    a. Fondaparinux has selective binding to factor Xa.
    b. Fondaparinux has high bioavailability.
    c. Fondaparinux has increased biological variability.
    d. Fondaparinux has potential minimization of immunogenic reactivity.
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