Development of a Synthetic Heparin Pentasaccharide: Fondaparinux

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ABSTRACT

Fondaparinux (Arixtra®; Sanofi-Synthélabo/Organon) is the first of a new class of antithrombotic agents distinct from low molecular weight (LMW) heparins and heparin. It is a synthetic pentasaccharide mimicking the site of heparin that binds to antithrombin III (AT). It is homogeneous with a molecular weight of 1728 Da. It exhibits only factor (F) Xa inhibitor activity via binding to AT, which in turn inhibits thrombin generation. It does not inhibit thrombin, release TFPI, or possess other actions of heparin. Low AT levels can limit the efficacy of fondaparinux. There is nearly complete bioavailability subcutaneously, rapid onset of action, a prolonged half-life (15-20 h) and no metabolism preceding renal excretion. Elderly and renal impaired patients have reduced clearance. The PT, aPTT and ACT are not affected by fondaparinux; anti-FXa assays are used if needed. Phase IIb clinical studies have identified a fixed dose of 2.5 mg once daily for prophylaxis of venous thrombosis without monitoring. Four phase III studies (n > 7000) demonstrated a combined 55% relative risk reduction of venous thromboembolic events in orthopedic surgery patients in comparison to the LMW heparin enoxaparin. Hemorrhagic complications for fondaparinux were either comparable to or higher than that for LMW heparin. The US FDA and the European CPMP have approved fondaparinux for prophylaxis of venous thrombosis after orthopedic surgery with limitations of use in elderly, low weight, renal impaired patients and in those receiving spinal anesthesia. Marketing is expected in Spring 2002. Clinical trials for treatment of established thrombosis, coronary syndromes and adjunct to thrombolytic therapy are in progress.

Key Words: Fondaparinux, Heparin.

The development of the chemically synthetic pentasaccharide as an antithrombotic drug was undertaken by Jean Choay and colleagues (Figure 1). From studies conducted during the late 1970's and early 1980's on fractions of heparin obtained via degradation and isolation procedures, it was deduced that a pentasaccharide was the minimal sequence of heparin able to activate antithrombin III (AT) to produce the inhibition of factor Xa (FXa) (Table 1)[1-4]. However, the structure of this five-unit saccharide chain needed to be of a specific sequence incorporating four specifically placed sulfate groups for optimum binding to AT, i.e., the 6-O sulfate on the D

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Figure 1. The Choay Group: Maurice Petitou (left), Jean Choay (center) and Jean-Claude Lormeau (right) which undertook the development of the pentasaccharide as antithrombotic drug.

unit, the 3-O sulfate on the F unit and two 2-N sulfates on the F and H units. This pentasaccharide (SR90107A/ Org31540; fondaparinux sodium; Arixtra®), characterized as a synthetic and selective FXa inhibitor, is the first of a new class of antithrombotic drugs and is being clinically developed through a cooperative effort between Sanofi-Synthélabo and Organon (Figure 2)[5,6].

BIOLOGICAL ACTIVITIES

Fondaparinux is different from heparin and low molecular weight (LMW) heparin (Table 2,3). It is a homogeneous substance (1728 Da) composed of one specific 5-unit saccharide. Fondaparinux is a selective and reversible inhibitor of FXa dependent on binding to AT to elicit its activity (Figure 3). It does not inhibit thrombin, and it does not release TFPI[7-9]. Other mec-

Table 1. Development of the synthetic heparin pentasaccharide

1968, 1973	AT is heparin cofactor	Abildgaard, Rosenberg
1976	Only part of UFH binds to AT	Andersson, Lam, Hook
1976	Anti-Xa activity of UFH independent of molecular size; anti-IIa activity dependent on UFH chain length	Andersson
1979	Tetrasaccharide suggested as the minimal sequence to bind AT and elicit anti-Xa activity	Rosenberg
1980	Ethanol precipitation and characterization of oligosaccharides from plasma	Choay, Lormeau, Casu
1981-2	Hypothesis that hexasaccharide was minimal sequence to bind AT and elicit anti-Xa activity	Choay, Lindahl
1981-2	Pentasaccharide represented the smallest heparin molecule to exhibit anti-Xa activity	Choay, Lindahl
1983-84	Synthetic production of a heparin pentasaccharide	Sinay, Petitou, van Boeckel
1986	Synthesis of a-methyl glycoside of the heparin pentasaccharide	Petitou, van Boeckel
1986	Antithrombotic activity of a pure anti-Xa active pentasaccharide established	Walenga
1987	Biological characterization of pentasaccharide	Walenga
1988	Critical role of the 3-O sulfate group for antithrombotic activity established	Walenga
1991-93	Series of structural analogues of pentasaccharide synthesized	Petitou, van Boeckel
1995	Clinical trials in orthopedic surgery begun	Sanofi-Organon
1995-present	Biologic characterization of pentasaccharide and related analogues	Lormeau, Herbert
2001	Publication of first phase IIb clinical trial	Turpie
2001	Publication of two first phase III clinical trials	Eriksson, Bauer

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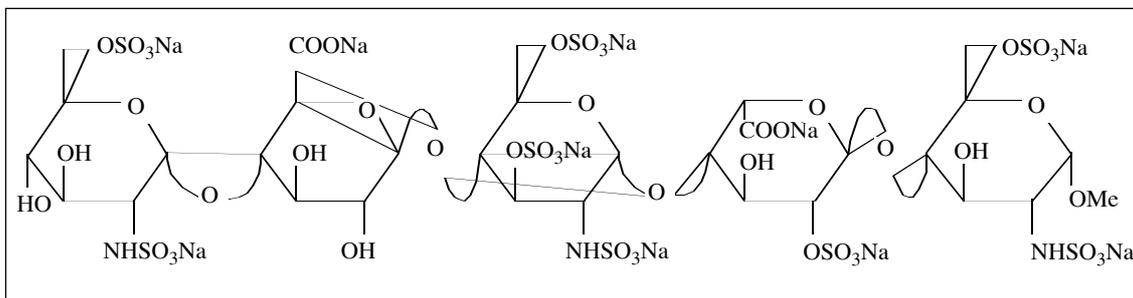Walenga JM, Fareed J, Jeske WP, Frapaise FX, Bick RL, Samama MM.

Figure 2. Fondaparinux (pentasaccharide; Org31540/SR90107A; Arixtra®; Sanofi-Synthélabo/Organon) is composed of the specific sequence of saccharide units required for heparin binding to AT and expression of a strong antifactor Xa activity. Based on the data from four phase III clinical trials, the US FDA and the European CPMP have approved fondaparinux for the prophylaxis of deep venous thrombosis in patients undergoing surgery for hip fracture, hip replacement and knee replacement. Trials are in progress for other clinical indications.

hanisms have been suggested such as inhibition of FVIIa, tissue factor-FVIIa complex and FIXa[10-13]. But it is unclear whether these are a direct effect by fondaparinux or an indirect effect due to FXa inhibition.

Since fondaparinux is completely dependent on binding to AT for expression of its anti-FXa effect (in a 1:1 molar ratio), low plasma concentrations of AT can be rate limiting for its activity[14]. In vitro studies demonstrated that for 0.5-2.0 μg/mL fondaparinux, at AT levels of 0.5 U/mL, there is 20% loss of activity in comparison to the activity obtained with 1.0 U/mL AT[15]. With 0.25 U/mL AT there is a 45% loss of activity and with 0.125 U/mL AT there is a 65% loss of fondaparinux activity. It should be considered that the antithrombotic effect of fondaparinux could be less in patients with either low levels of AT due to congenital deficiencies or consumption, or patients requiring high concentrations of fondaparinux, e.g., patients undergoing interventional procedures or patients with therapeutic dosing that results in plasma levels higher than 3 μg/mL.

Blocking the activity of FXa inhibits the generation of thrombin. Fondaparinux produces a dose-dependent inhibition of the amount of thrombin generated and a prolongation of the lag phase of thrombin generation[7,16,17]. There is a correlation between the anti-FXa activity, inhibition of thrombin generation and in vivo antithrombotic activity.

Fondaparinux does not cause platelet aggregation or influence platelet aggregation induced by the typical agonists[4,18]. It does not induce in vitro platelet aggregation/activation in the presence of heparin antibody obtained from patients clinically diagnosed with heparin-induced thrombocytopenia (HIT)[4,18-21]. However, data from the two published phase III trials in orthopedic surgery reveal that platelet counts < 100.000/mL do occur with fondaparinux treatment. In the fondaparinux groups 2.7% and 3.7 of patients developed thrombocytopenia compared to 4.9% and 5.3% of patients treated with enoxaparin in the same studies[22,23].

PRECLINICAL STUDIES

Fondaparinux produces a dose-dependent inhibition of venous thrombosis in animal models[4,21,24-27]. In subcutaneous studies the dose of fondaparinux was only 1.5-fold higher than the dose in the intravenous studies to block the same thrombosis endpoint[24]. On the other hand, a nearly 6-fold higher dose of subcutaneous heparin was required to achieve the same thrombosis inhibition endpoint[24].

Fondaparinux was effective at inhibiting platelet deposit and platelet rich thrombus growth in models of arterial thrombosis after intravenous administration. A relatively high dose, higher than required to suppress venous thrombosis (> 250 μg/kg), was required[24,27-30].

HEMORRHAGIC EFFECTS

Fondaparinux administered to rats at high doses of 25 mg/kg produced only a 2-fold increase in blood loss. In comparison, heparin produced a 5-fold increase in blood loss at approximately 2 mg/kg[27]. In a rabbit model, fondaparinux did not significantly increase the

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Table 2. Characteristics of fondaparinux

• Synthetic

• Defined, pure, homogeneous molecular structure

• No viral or other animal contaminants

• Batch to batch consistency

• High affinity for AT

• Requires AT for effect

• Selective; single target FXa inhibition

• Inhibits thrombin generation

• Thrombin generation is correlated with in vivo antithrombotic activity

• Chromogenic or clot-based anti-FXa assays can be used to measure plasma levels

• Antithrombotic activity well-documented in animal models

• Proven efficacy for prophylaxis against VTE

• Bleeding not reduced from that of LMWHs

• Higher bleeding risk than predicated by animal models

• Nearly 100% bioavailability by sc route

• Half-life is 15-20 hours

• Half-life is extended when bound to AT

• Limited distribution throughout body

• Volume of distribution similar to that of blood volume

• Rapid onset of action

• Not metabolized

• Excreted in uring unchanged

• Steady state is reached 3-4 days after repeated dosing

• Low inter-subject variability in normals

• Elderly have increased half-life and decreased clearance

• Drug accumulation in patients with renal dysfunction

Table 3. Characteristics of heparin not associated with fondaparinux

• Antithrombin activity

• Inhibition of serine proteases other than FXa

• HCII interaction

• TFPI release

• Effect on the aPTT

• Fibrinolytic activity

• Cross-reaction with heparin antibody

• PF4 interaction

• Neutralization by protamine

• Established antidote for bleeding

• Traditional assays for heparin monitoring cannot be used

amount of blood loss at doses 50-fold higher than the dose producing an antithrombotic effect[24]. In comparison, heparin significantly increased blood loss at a dose 10-fold higher than that which completely inhibited clot formation. No bleeding effect was observed in a baboon model[29].

In human volunteers, the bleeding time test remained normal with repeated single daily injections of 11.4 or 26.6 mg fondaparinux[31]. Only minor hematomas at the injection/cannula site, mild transient hematuria and rebleeding in one patient occurred.

In contrast to the weak bleeding effect observed in the animal and preclinical studies in young, healthy individuals, a bleeding risk was observed in the clinical studies. In the phase IIb dose finding clinical trial of fondaparinux in orthopedic surgery, major bleeding
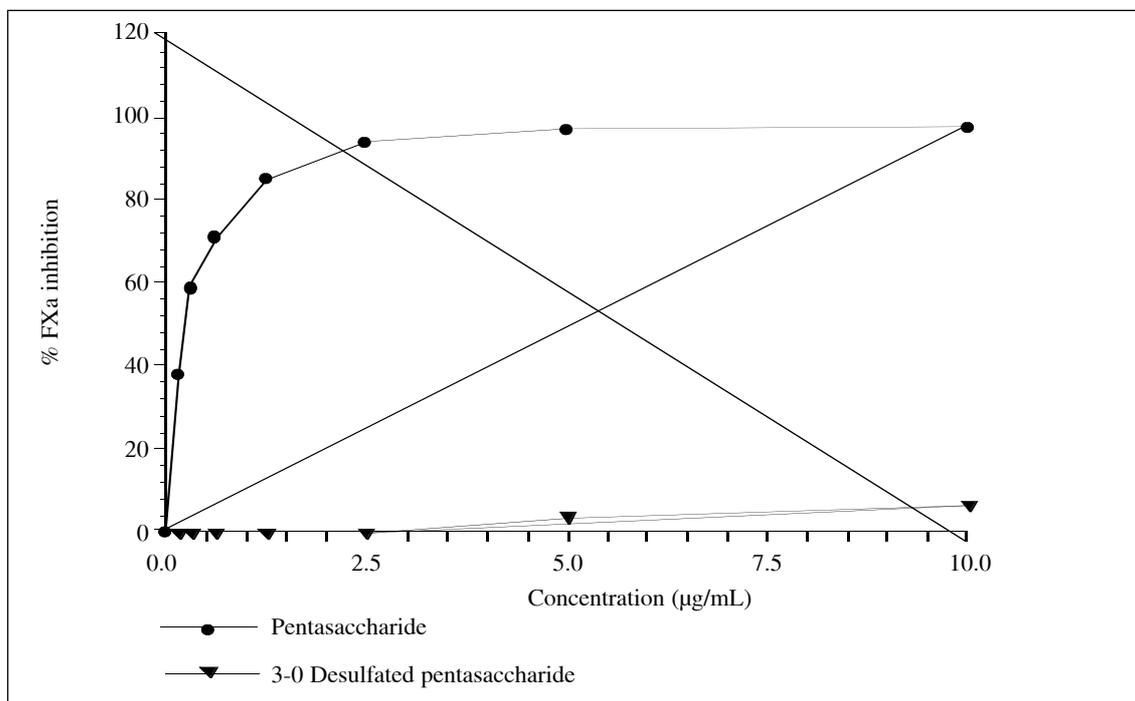
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Figure 3. Dose-response of fondaparinux in the chromogenic antifactor Xa assay. The specific structure of fondaparinux that allows binding to AT is critical for expression of the anti-FXa activity as shown by the loss of activity by a pentasaccharide of the same structure but without the 3-O sulfate group on the F unit.

was evident and dose-dependent[32]. Fondaparinux at 3 mg once daily produced slightly but not significantly higher bleeding in comparison to 30 mg bid enoxaparin. At 6 and 8 mg fondaparinux, significant major bleeding occurred.

In the PENTAMAKS clinical trial, major bleeding with fondaparinux (2.5 mg single daily sc dose) was significantly more frequent than with enoxaparin (p< 0.006)[23]. In the PENTHIFRA clinical trial minor bleeding with fondaparinux was more frequent than with enoxaparin (p= 0.02)[22]. Thus, no reduction in the bleeding risk of fondaparinux compared to LMW heparin was demonstrated.

Analysis of the phase III trial data determined that if the first injection of fondaparinux was given < 6 hours after skin closure postoperatively (n= 1337) there was significantly more bleeding than if fondaparinux was given 6 hours after skin closure (n= 2230) (3.0 vs 1.8%; p= 0.028)[33].

PHARMACOKINETICS

The half-life of fondaparinux is 15-20 hours[31,34-

36]. According to van Amsterdam, the binding of fondaparinux to AT governs its pharmacologic profile and extends the half-life of AT-bound fondaparinux[37]. There is subcutaneous bioavailability of nearly 100% with limited distribution in the body consistent with the blood volume[27,38]. There is a rapid onset of action as 1/2 maximum activity is reached within 25 minutes after subcutaneous administration and a peak concentration is reached in 2 hours[38]. Area under the curve (AUC) and clearance (C_{max}) correlate linearly with dose[31].

There is no evidence of metabolism. Fondaparinux is predominantly cleared through the kidneys[38]. The renal clearance rate of non-AT-bound fondaparinux is < 10 minutes[37]. Steady state plasma concentrations are reached 3-4 days after repeated daily administration of single doses of 2, 4 or 8 mg sc fondaparinux[38]. In normal individuals, low inter-subject variability is observed.

In healthy, elderly subjects fondaparinux shows certain significant differences from the pharmacokine-

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tics of healthy, young individuals[31]. The mean half-life was prolonged (13.6 vs 15.9 h for young vs elderly respectively; p< 0.01); the mean AUC was larger (19.4 vs 25.0 µg/mL/h); the mean plasma clearance was lower (7.5 vs 5.5 mL/min; p< 0.001); the amount of drug recovered in the urine during the 24 hours after injection and the renal clearance were reduced (p< 0.001)[31].

In a study of young and elderly individuals, highly significant correlations were found between creatinine clearance and plasma clearance of fondaparinux (r= 0.61; p< 0.001) or renal clearance of fondaparinux (r= 0.73; p< 0.001)[31]. These findings were verified in a phase I trial in 20 subjects with varying renal impairment where creatinine clearance and fondaparinux clearance were linearly related (r= 0.89; p< 0.001)[39].

One study of the in vitro protein binding of fondaparinux showed 97% bound to plasma AT and > 94% bound to purified AT (0.125 mg/mL)[40]. The protein-binding fractions were comparable between plasma AT and purified AT systems, and decreased at higher concentrations of fondaparinux. No binding to albumin or a1-acid glycoprotein was detected.

An in vitro model of human placental transfer showed that at concentrations corresponding to plasma levels obtained in the acute treatment of venous thrombosis, both fondaparinux (1.75 µg/mL) and enoxaparin (1 anti-FXa U/mL) were not detected in the fetal venous effluent (n= 15)[41].

Fondaparinux cannot be neutralized with protamine sulfate[4,21]. Heparinase I and II, but not III, produce a concentration-dependent inhibition of the in vivo antithrombotic activity of fondaparinux[42-44]. Heparinase I is currently under development for clinical use. Activated prothrombin complex concentrates and recombinant FVIIa were shown to restore hemostasis in animals administered fondaparinux[45].

To date several drug interaction studies of subcutaneous fondaparinux have been conducted. No alterations of the pharmacokinetic/pharmacodynamic profile of fondaparinux have been observed when coadministered with the oral nonsteroidal antiinflammatory piroxicam, warfarin or aspirin[46-48].

LABORATORY MONITORING

Fondaparinux has no effect on the prothrombin time (PT) or thrombin clotting time[21]. Prolongation of the activated partial thromboplastin time (aPTT) is only weakly observed with concentrations < 5.0 µg/mL[20]. Laboratory monitoring of fondaparinux is currently not being recommended for prophylactic dosing. If necessary, fondaparinux can be measured by the chromogenic anti-FXa assay, Heptest® (Haemachem; St. Louis, MO) or other clot-based anti-FXa assays available in special hematology labs.

CLINICAL TRIALS (Table 4)

Prophylaxis of VTE

The PENTATHLON study was a double-blind, randomized, multi-center phase IIb dose-ranging clinical trial for fondaparinux in elective hip replacement patients (n= 933)[32]. Fondaparinux given once daily for 5-10 days was started 6 ± 2 hours postsurgery, whereas in the control enoxaparin group (30 mg bid) treatment was started 12-24 hours postoperatively.

The efficacy results showed a dose-dependent decrease of venous thromboembolic events (VTE) for fondaparinux dosages of 0.75 (11.8%; n= 119), 1.5 (6.7%; n= 120) and 3.0 (1.7%; n= 115) mg once daily as determined by bilateral venograms on day 5-10[32]. The 6 mg group (4.4%; n= 45) had a higher incidence of VTE than the 3 mg group; the 8 mg group (n= 23) had no VTE. A significant reduction in the incidence of VTE relative to enoxaparin (9.4% VTE; n= 171; p= 0.01) was observed only with 3 mg fondaparinux with a relative risk reduction (RRR) of 82%.

Major bleeding increased with increasing dose of fondaparinux. Slightly, but not significantly, higher major bleeding was found with 3 mg fondaparinux (n= 177) in comparison to enoxaparin (n= 260) (4.5 vs 3.5%)[32]. The 6 mg and 8 mg fondaparinux groups were discontinued after 9/72 (16.7%) and 6/52 (17.3%) patients, respectively, reported major bleeding episodes.

Four randomized, double-blind, phase III clinical trials designated PENTHIFRA, PENTATHLON 2000, EPHESUS, and PENTAMAKS were designed in parallel[22,23,49,50]. Fondaparinux was dosed subcutaneously at 2.5 mg per day for a maximum of 9 days with the first injection initiated 6 ± 2 hours after surgery and the second 12 or more hours after the first.

The PENTHIFRA study was conducted in 1711 patients undergoing surgery for fracture of the upper

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third of the femur[22]. Enoxaparin, the comparator drug, was dosed at 40 mg sc bid with the first dose 12 ± 2 hours preoperatively and second dose 12-24 hours postsurgery. Fondaparinux (8.3%; n= 52/626) was more effective than enoxaparin (19.1%; n= 119/624) in preventing VTE by day 11 (confirmed by venography, V/Q scan, angiography, spiral-computed tomography or autopsy) with a 56% RRR (p< 0.001). The number and type of major bleeding episodes was similar for both drugs (18/831 or 2.2% for fondaparinux; 19/842 or 2.3% for enoxaparin). Minor bleeding was significantly more frequent in the fondaparinux group (4.1 vs 2.1%; p= 0.02).

The PENTATHLON 2000 study of primary total hip replacement or revision surgery was conducted in 2275 patients[49]. Enoxaparin was dosed at 30 mg sc twice daily, starting 12-24 hours postoperatively. The RRR for the prevention of VTE by fondaparinux was not significant at 26% (n= 1584 evaluable patients; p= 0.099). Although the safety profile for most clinically relevant bleeding was stated to be similar for both drugs, no data has been published.

The EPHESUS study of primary total hip replacement or revision surgery was conducted in 2309 patients[50]. Enoxaparin was dosed according to the standard European regimen starting with 40 mg presurgery, then 40 mg sc daily postoperatively. Fondaparinux was more effective in preventing VTE with a 56% RRR (4.1 vs 9.2%; n= 1827 evaluable patients; p< 0.001). Although the safety profile was stated to be similar for both drugs, no data has been published.

The PENTAMAKS study of elective major knee surgery was conducted in 1034 patients[23]. Enoxaparin was dosed according to the standard North American regimen as in PENTATHLON 2000. Fondaparinux (12.5% VTE; n= 45/361) was more effective than enoxaparin (27.8% VTE; n= 101/363) in preventing VTE with an overall 55% RRR (p< 0.001). Major bleeding occurred more frequently in the fondaparinux group (11/517 or 2.1% vs 1/517 or 0.2%; p= 0.006).

Treatment of VTE

The REMBRANDT trial was a phase II study for treatment of symptomatic DVT. Fondaparinux (5, 7.5 or 10 mg once daily for an average 6-7 days; n= 334) was compared to the LMW heparin dalteparin (100 IU/kg twice daily; n= 119)[51]. The primary efficacy outcome was a change in thrombus mass assessed by ultrasonography of the leg veins and V/Q scan of the lungs on day 7 ± 1. Improvement was observed in 46%, 48% and 42% of the fondaparinux treatment groups vs 49% for dalteparin. There were 8/334 (2.4%) recurrent thromboembolic complications in the fondaparinux patients and 6/119 (5.0%) in the dalteparin patients, a 2.6% difference in favor of fondaparinux. Bleeding was similar among the groups.

Two phase III clinical trials for treatment of established thrombosis were designed to study the safety and efficacy of 7.5 mg daily fondaparinux. The MATISSE DVT trial will compare fondaparinux to enoxaparin in a double-blind study of 2200 patients, and the MATISSE PE trial will compare fondaparinux to heparin in an open study of 2200 patients.

Other Clinical Indications

Fondaparinux does not possess any thrombolytic activity in itself, but it may be a useful adjunct to thrombolytic therapy as suggested by animal studies[52-54]. PENTALYSE was a phase IIb dose-ranging study of fondaparinux as an adjunct anticoagulant to alteplase and aspirin in acute ST-segment elevation myocardial infarction (MI)[55]. Patients (n= 333) were randomized to either heparin given intravenously during the first 48-72 hours or one of three doses of fondaparinux administered intravenously on day 1 then subcutaneously daily for 5-7 days. It is unknown if there was a dose-response between three doses of fondaparinux. The primary safety endpoint of combined incidence of intracranial hemorrhage and need for blood transfusion was identical with fondaparinux and heparin (7.1%). One nonfatal intracranial hemorrhage occurred in the fondaparinux group (0.4%).

A pilot trial in conventional balloon coronary angioplasty (n= 61) showed that a 12 mg fondaparinux infusion, with 500 mg IV aspirin, was safe and effective with only 3.3% abrupt vessel closures within 24 hours of the procedure[56]. There was no major bleeding. The plasma levels of fondaparinux were 1.91 ± 0.39 µg/mL at 10 minutes and 0.36 ± 0.11 µg/mL at 23 hours. During and after the procedure the ACT and aPTT remained within the normal range. This study showed that fondaparinux was at least as effective as heparin in interventional cardiology procedures.

The PENTUA trial (Pentasaccharide in Unstable

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Table 4. Clinical trials with fondaparinux

Clinical trial	Patient population	Control drug	Thrombosis (%)		Bleeding (%)	
			Fondaparinux	Control	Fondaparinux	Control
Venous Thrombosis Prophylaxis						
Pentathlon[13]	Hip replacement surgery	Enoxaparin	1.7% VTE for 3 mg	9.4% VTE p< 0.001	4.5% major for 3 mg; 6 and 8 mg D/C	3.5% major
Ephesus[15]	Hip replacement surgery (elective)	Enoxaparin	4.1% VTE 56% RRR	9.2% VTE p< 0.001	Not published	Not published
Penthifra[16]	Hip fracture surgery (trauma)	Enoxaparin	8.3% VTE 56% RRR	19.1% VTE p< 0.001	4.1% minor; p= 0.02	2.1% minor
Pentathlon 2000[14]	Hip replacement surgery (elective)	Enoxaparin	6.2% VTE 26% RRR	8.3% VTE p= 0.099	Not published	Not published
Pentamaks[17]	Major knee surgery (elective)	Enoxaparin	12.5% VTE 55% RRR	27.8% VTE p< 0.001	2.1% major; p= 0.006	0.2% major
Venous Thrombosis Treatment						
Rembrant[49]	DVT treatment	Dalteparin	2.4% recurrent thrombosis	5.0% recurrent thrombosis	No significant difference	
Matisse DVT	DVT treatment	Enoxaparin	--	--	--	
Matisse PE	PE treatment	Heparin	--	--	--	
Cardiology						
Pentalyse[53]	Adjunct to tPA/aspirin for AMI	Heparin	No significant difference		No significant difference	
Vuillemenot, et al.[54]	PTCA with aspirin	None	2 acute vessel closures	--	No major	--
Pentual[55]	Unstable angina, non-Q wave MI	Enoxaparin	No significant difference		No significant difference	

D/C: Discontinued, VTE: Venous thromboembolic event, RRR: Relative risk reduction, AMI: Acute myocardial infarction, PTCA: Percutaneous transluminal coronary angioplasty.

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Angina) trial is a phase IIb study of the efficacy of fondaparinux for the treatment of unstable angina or non-Q wave myocardial infarction[57]. The 2.5 mg/day dose group had an event rate of 30% in comparison to 40% for the standard dose of enoxaparin. The 4, 8 and 12 mg once daily doses of fondaparinux failed to do as well and were associated with additional bleeding episodes. When data from all doses of fondaparinux were combined into one group, the event rate increased to 37%.

REGULATORY STATUS

On December 10, 2001 the US FDA granted approval for fondaparinux (Arixtra®) for the prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery and knee replacement surgery. The FDA stated that fondaparinux cannot be given to patients with kidney failure and those with weight < 110 lbs due to a risk of serious bleeding. The hemorrhagic risk also increases with age. The epidural/spinal anesthesia or spinal puncture contraindication is also extended to fondaparinux, grouping it in the same category as LMW heparins. On the basis of the current clinical trials the US FDA did not acknowledge the superior claim for fondaparinux in reference to enoxaparin. On December 14, 2001 the Committee of Proprietary Medical Products (CPMP) recommended marketing authorization for fondaparinux in the European Union with dosing recommendations consistent with those of the US dosing. Marketing is expected in Spring of 2002.

FONDAPRINUX vs LMW HEPARIN

Fondaparinux essentially represents the oligosaccharide consensus sequence of heparin, which is capable of binding to AT, facilitating FXa/thrombin generation inhibition actions. The very discovery of oligosaccharides with the AT binding consensus was based on the isolation of ethanol precipitated oligosaccharides from fractionated or depolymerized LMW heparins. Such oligosaccharides are present in varying proportions in the available LMW heparin preparations. Thus, fondaparinux represents a purified and concentrated homogenous oligosaccharide with strong affinity to AT.

Fondaparinux is a heparin-mimetic; however, it is distinct from heparin and LMW heparin. To compare fondaparinux to LMW heparins, several fundamental and biological considerations may be taken into account. Fondaparinux is a synthetic homogenous oligosaccharide with defined chemical characteristics, whereas LMW heparins represent a diverse group of drugs that are prepared upon digestion of porcine mucosal heparin. Not only do the LMW heparins vary in their molecular composition, but they exhibit diverse pharmacologic actions including interactions with AT and HCII, release of TFPI, antithrombin and profibrinolytic actions, antiinflammatory targets, interactions with growth factors, modulation of adhesion molecules and endothelial cell effects. Based on its structure-activity relationships fondaparinux will not exhibit all these biological actions. However, there may be certain endogenous biological actions of fondaparinux independent of its interaction with AT that may be responsible for some of its effects.

Since thrombogenesis is a poly-pathologic process where multiple targeting of cellular and plasmatic sites may be important, fondaparinux may have a narrow spectrum in comparison to LMW heparins. Although in the reported clinical trials fondaparinux, at a relatively lower dosage, exhibited a superior therapeutic efficacy in comparison to a specific LMW heparin, the relative hemorrhagic effects of fondaparinux were in several instances higher than the comparator drug. Thus, the therapeutic index of fondaparinux is relatively narrow in comparison to LMW heparins. The relative hemorrhagic risks at a low dose, and the absence of a clear-cut dose therapeutic response in several clinical trials, require additional studies to understand these observations.

LMW heparins are now proven to be effective in expanded indications in both thrombotic and cardiovascular disorders. This is due to their poly-pharmacologic actions. The results for fondaparinux in such clinical settings as acute coronary syndrome have not shown superiority over LMW heparins. Thus, whether fondaparinux will exhibit a similar expanded therapeutic spectrum as LMW heparins remains an open question.

Synthetic agents have certain advantages over naturally derived products not the least of which is their specific chemical design to target desired biological effects. The direct anti-FXa actions and the homogeneity

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of fondaparinux make its pharmacokinetics predictable. If there remain serious efficacy limitations of fondaparinux, oligosaccharide conjugates expressing additional actions such as antithrombin and TFPI release may be developed to provide a synthetic drug with a comparable pharmacologic and clinical profile as the natural heparins. It may also be possible to combine fondaparinux with other anticoagulant/antithrombotic agents to achieve desired therapeutic actions, as has been done in the case of clopidogrel and aspirin.

SUMMARY

Fondaparinux (Arixtra®; Sanofi-Synthélabo/Organon) is the first of a new class of antithrombotic agents. Prophylaxis with fondaparinux resulted in a 55% relative risk reduction of venous thrombosis in clinical trials; however, the bleeding risk with fondaparinux was not reduced from that of LMW heparin. The US FDA and the European CPMP have recently approved fondaparinux for the prevention of venous thromboembolic events following orthopedic surgery.

Although a heparin-mimetic and dependent on AT to inhibit FXa and therefore thrombin generation, fondaparinux is distinct from heparin and LMW heparin. It only exhibits a monotherapeutic pharmacologic action of heparin, namely the anti-FXa effect. It is devoid of other therapeutic effects of heparins such as the release of TFPI, anti-thrombin, profibrinolytic and antiinflammatory actions.

The synthetic nature of fondaparinux provides for a pure material of one known chemical structure with no biological and pharmacological differences between batches. It is characterized by complete subcutaneous bioavailability, a rapid onset of action, no evidence of metabolism and renal excretion. To date no drug interactions or nonspecific protein binding have been found with fondaparinux. However, the reported predictable pharmacokinetics are based on studies in normal volunteers and in relatively healthy orthopedic patients. Whether this pharmacokinetic profile remains in sicker populations where variations in patient weight occur, AT levels fluctuate with the disease process or with interventional procedure/surgery, and renal dysfunction or liver disease are common is unknown.

Based on the 15-20 hour half-life, once a day dosing and no monitoring are currently being recommended for clinical use. This drug does not affect the aPTT, PT or ACT assays. Drug levels can only be determined by anti-Xa assays.

The lack of dose-efficacy response in different clinical trials deserves further investigation, as there is no clear explanation for these observations. The interpretation of the bleeding and thrombosis rates observed with fondaparinux and LMW heparin in the VTE prevention trials has already been questioned in public forums and in print[58]. Because the study designs did not allow for a valid comparison from a pharmacologic standpoint, it is unclear whether the differences between fondaparinux and enoxaparin are due to the drugs themselves or to the dosing regimen (e.g., LMW heparin starting 12-24 h after surgery, fondaparinux starting 6 ± 2 h after surgery).

The observed bleeding in the clinical trials and the limitations imposed by the FDA and the CPMP questions the appropriateness of the fixed dosing regimen without monitoring. The long half-life may have an effect on drug accumulation. Unlike heparin, the effects of fondaparinux cannot be neutralized by conventional methods. There may be patient subpopulations that will require monitoring for safety and efficacy reasons.

How and where fondaparinux is used clinically, and how it will compete with LMW heparins, direct thrombin inhibitors and direct FXa inhibitors to combat the various types of clinical thromboses remain to be determined.

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