Fondaparinux in Acute Coronary Syndromes

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Abstract

Anticoagulant therapy is a major component in the management of acute coronary syndromes (ACS). Anticoagulant-associated adverse events like heparin-induced thrombocytopenia, bleeding complications and need of close monitoring of anticoagulation led to focus on developing agents causing anticoagulation without affecting primary haemostasis. Fondaparinux, a new-age synthetic anticoagulant, acts by inhibiting factor Xa. It is simple to administer and has low inter and intra-subject variability. Moreover, there is no risk of significant drug interactions and no need for monitoring the platelet count. Efficacy of fondaparinux has been studied in various disorders including prevention of venous thromboembolism in major orthopaedic surgery, abdominal surgery and acutely ill medical patients, treatment of venous thromboembolism, non-ST-elevation acute coronary syndromes and ST-elevation acute myocardial infarction. This article covers the review of fondaparinux and its practical advantages mainly in the management of ACS including non-ST-elevation acute coronary syndromes and ST-elevation acute myocardial infarction.

Introduction

Risk of venous thromboembolism is well recognized as a postoperative complications in major orthopaedic surgery involving lower limbs like hip replacement or knee replacement. In such cases, prophylactic use of anticoagulants significantly reduces the risk of venous thromboembolism.¹ Similarly, anticoagulant therapy is a major component in the management of acute coronary syndromes (ACS).² The anticoagulants may impose many limitations for their usage in clinical practice including chances of adverse events like heparin-induced thrombocytopenia, bleeding complications and need of close monitoring of anticoagulation. These concerns led to focus on the development of agents which can cause anticoagulation and at the same time do not affect the primary haemostasis.³

As factor Xa is the major target for developing anticoagulant agents,² a synthetic pentasaccharides which can specifically inhibit factor Xa activity and produce an antithrombotic effect without causing inhibition of factor IIa or antiplatelet activity has been discovered.¹

Fondaparinux

Fondaparinux is a synthetic, factor Xa inhibitor which is structurally similar to the antithrombin binding site of heparin and low-molecular-weight heparin (LMWH).³ The inhibition of factor Xa is mediated by plasma antithrombin.² Through its unique mechanism of action, fondaparinux attaches to the antithrombin and changes its structure leading to inhibition of factor Xa. The affinity of fondaparinux for antithrombin is 15 times higher as compared to unfractionated heparin.³ Compared to heparins, fondaparinux offers advantages due to its selective binding to antithrombin and rapid and predictable inhibition of factor Xa. It shows low interindividual and intraindividual variability. There is no need of laboratory monitoring with the use of fondaparinux.³

Major Pharmacokinetic and Pharmacodynamic Properties

Fondaparinux can be administered by intravenous or subcutaneous route.² Subcutaneously administered fondaparinux sodium 2.5 mg has been shown to be rapidly and completely absorbed in healthy volunteers¹ with 100% bioavailability.⁵ The mean maximum plasma concentration is achieved in a mean time of 1.7 hours.¹ With intravenous dosage, the maximum plasma concentration of fondaparinux is achieved even faster as compared to subcutaneous administration, without any effect on the half-life.⁶ The mean elimination half-life of fondaparinux is 17.2 hours, which allows once daily administration¹ and also result in maintenance of significant,² predictable and

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sustained\(^7\) anticoagulant activity for 24 hours.\(^2\) There is no need for any dose adjustment or dose monitoring in most of the patients in routine practice,\(^8\) providing significant benefit for the clinician using it. However, in special populations, if required, fondaparinux monitoring should be done quickly with a validated commercially available anti-Xa assay using fondaparinux calibrators.\(^9\)

Kidney is the main elimination route of fondaparinux sodium through which it is mainly excreted unchanged.\(^1\) Studies in healthy volunteer have shown that fondaparinux sodium does not have pharmacokinetic interaction with warfarin\(^10\) and aspirin.\(^1\) Thus, the pharmacokinetic properties, pharmacodynamic effects and route of administration offer remarkable advantages and simplify the treatment making administration more convenient.\(^7\)

**Dose of Fondaparinux**

The recommended dose of fondaparinux for the treatment of ACS is 2.5 mg.\(^8\) The dose of fondaparinux 2.5 mg once daily subcutaneously is selected based on the dose-ranging study. In the Pentasaccharide in Unstable Angina (PENTUA) study, fondaparinux was administered subcutaneously in four different dosages 2.5, 4, 8, or 12 mg once daily and efficacy of different dosages was compared with enoxaparin 1 mg/kg twice daily given for three to seven days, in ACS without persistent ST-segment elevation. The results of this study showed no dose response.\(^11\)

**Efficacy of Fondaparinux**

The efficacy and safety of fondaparinux has been evaluated in many clinical studies. It has been found to be effective and well tolerated in prevention of various thromboembolic conditions.

**Efficacy in Acute Coronary Syndrome**

Two pivotal studies were conducted to evaluate the efficacy of fondaparinux in ACS management. The OASIS-5 trial was conducted in patients with non-ST-elevation ACS (NSTE-ACS) while the OASIS-6 trial was performed in ST-elevation myocardial infarction (MI).

**The OASIS-5 Trial**

Selecting a right anticoagulant in patients with NSTE-ACS is critical. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) study\(^12\) evaluated the comparative efficacy and safety of fondaparinux versus enoxaparin in this condition. The primary efficacy outcome in the study was death, myocardial infarction, or refractory ischemia. The study proved its objective of showing non-inferiority of fondaparinux versus enoxaparin by demonstrating similar primary outcome events in both group at nine days (Figure 1). Thus, in patients with acute coronary syndrome, the efficacy of fondaparinux was found to be similar to enoxaparin in reducing the risk of ischemic events at nine days. It also improves long term mortality and morbidity.

The combined use of anticoagulant and antiplatelet agents with invasive procedure reduces ischemic events in high-risk patients with acute coronary syndromes. However, there are concerns of increased bleeding and higher risk of complications like myocardial infarction, stroke and even death. In light of this the results of this trial make fondaparinux an attractive option for the patients with acute coronary syndrome.\(^12\)

**Place of Fondaparinux in the Management of ACS**

In the European Society of Cardiology (ESC)\(^13\) as well as American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines\(^14\) on the management of patients with NSTE-ACS, use of an anticoagulant drugs has class IIA recommendation. Thus, fondaparinux has class I recommendation in both the ESC and ACC/AHA NSTE-ACS guidelines. As per ESC guidelines, in case of pending decision between early invasive or conservative strategy, fondaparinux was
preferred based on its better efficacy/safety profile.13

**The OASIS-6 Trial**

The OASIS-6 was a randomized double-blind comparative trial of fondaparinux 2.5 mg once daily versus control group for up to 8 days in ST-elevation acute myocardial infarction (STEMI). A total of 12,092 patients were enrolled in the study.15 In STEMI, especially patients not undergoing primary percutaneous coronary intervention, fondaparinux significantly reduces mortality and reinfarction. The results of OASIS-6 trial showed significantly less incidence of death or reinfarction at 9 days, 30 days and at the end of study compared to the control group (day 9, P=.003; day 30, P=.008; and at study end P=.008; (Figure 2).

Significant benefits i.e. reduction in death and reinfarction were seen in patients receiving thrombolytic therapy and patients not receiving any reperfusion therapy.

A French registry of NSTEMI patients, predominantly managed invasively, has not shown superiority of fondaparinux versus enoxaparin in terms of bleeding events or 1-year mortality.16 An open label, study compared the safety and efficacy of enoxaparin and fondaparinux in patients with unstable coronary artery disease.17 Similar recovery was seen with both drugs. Numerically high, but statistically non-significant recurrent MI or angina was seen in patients receiving enoxaparin. At 30 days, there was higher incidence of haemorrhage in enoxaparin group. Patients with fondaparinux had no haemorrhage at day 30.

**Efficacy in Patients Undergoing Percutaneous Coronary Intervention (PCI)**

Factor Xa is a target for treatment of arterial thrombosis because of its important role in the formation of thrombin. In the ASPIRE trial involving 350 patients undergoing contemporary PCI, fondaparinux 2.5 and 5.0 mg was found to be comparable to UFH in terms of safety and efficacy outcomes. The incidence of total bleeding was 7.7% in the UFH group and 6.4% in the combined fondaparinux groups, with less incidence seen in 2.5 mg fondaparinux group compared to 5 mg fondaparinux group (3.4% versus 9.6%). There was no significant difference in efficacy of fondaparinux as compared with UFH.18

Thus, fondaparinux has particular advantages for use in acute coronary syndromes, and its efficacy and safety have been clearly demonstrated in two large randomized clinical trials in ACS.

A recent study in Chinese patients evaluated efficacy and safety of fondaparinux in combination with tirofiban in high-risk unstable angina patients undergoing complex PCI. The patients received either fondaparinux plus tirofiban or enoxaparin plus tirofiban. In both groups, there was no severe bleeding during hospitalization. However, patients in fondaparinux group has significantly lower incidence of mild and minor bleeding. The results of this study demonstrated good efficacy and safety of fondaparinux plus tirofiban combination in high-risk unstable angina patients undergoing complex PCI.19

Catheter-induced thrombosis in fondaparinux-treated patients undergoing PCI may be prevented by giving heparin as practiced in FUTURA/OASIS-8 trial.20

**Fondaparinux in Other Conditions**

The efficacy and safety of fondaparinux in preventing venous thromboembolism (VTE) during orthopedic surgery has been proved. Fondaparinux is at least as effective and safe as body-weight-adjusted enoxaparin in the initial treatment of symptomatic deep venous thrombosis (DVT). Fondaparinux offers a simple dosage regimen of once-daily subcutaneous dosage as compared to twice-daily dosage with enoxaparin.21 Fondaparinux is found to be superior to standard treatment in the prevention of venous thrombosis.18 In a retrospective review, fondaparinux has been shown comparable efficacy and safety to that of enoxaparin in preventing DVT and pulmonary embolism (PE) in patients with stroke. The demonstrated efficacy and safety of fondaparinux, makes it a potentially important option for the prevention of VTE in stroke.22

With daily monitoring of anti-Xa activity, fondaparinux may be used as an alternative for the management of heparin-induced thrombocytopenia in postoperative cardiac surgery patients as shown in a recently published retrospective study.23

**Fondaparinux in Pregnancy**

Heparin is considered as the drug of choice for the treatment or prevention of thromboembolic events during pregnancy.24 Fondaparinux does not cross the placenta. It belongs to pregnancy class B. It can be used in outpatients without need for monitoring.25 Though fondaparinux has been shown to be successfully used in case of severe allergic reactions to heparin, its use in pregnancy, should be limited to the patients with severe allergic reactions to heparin or those with heparin-induced thrombocytopenia, till larger studies are available.24

**Safety**

As fondaparinux does not cross-react with heparin-induced antibodies, the monitoring of platelet count may not be required.7 Similarly, it has been used successfully in cases with hypersensitivity to unfractioned
Fondaparinux has a positive benefit-risk ratio in the prophylaxis of venous thromboembolism in high-risk surgical and acutely ill medical patients. Its efficacy and safety is well demonstrated in various conditions that include initial treatment of symptomatic deep-vein thrombosis and pulmonary embolism, and in patients with non-ST and ST-elevation acute coronary syndromes. It can be used as an alternative to UFH or LMWH in the presence of hypersensitivity. This new-age anticoagulant provides various advantages including low inter and intra-subject variability, no risk of significant drug interactions, no need to monitor platelet count and simple administration.

**References**

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