Fondaparinux

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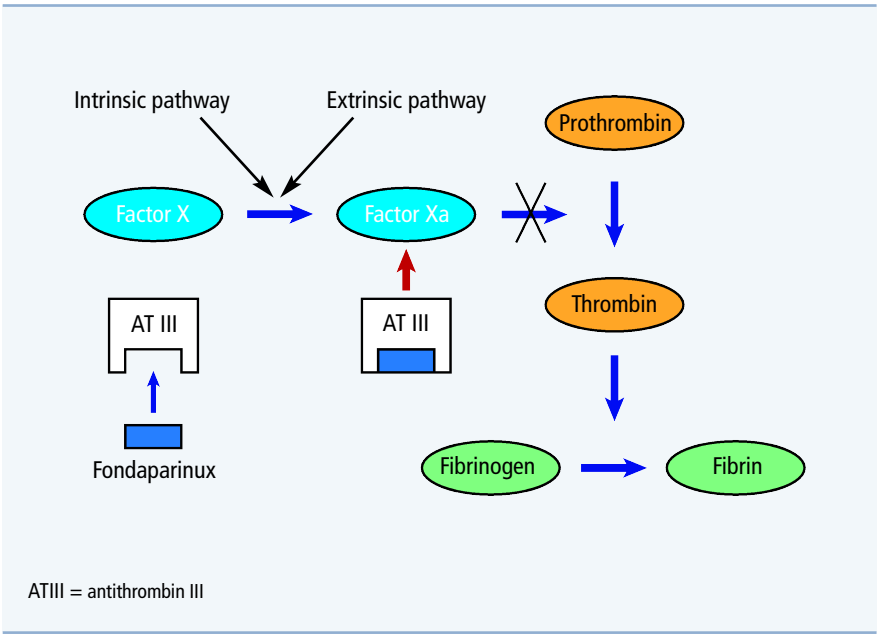

Figure 1. The pharmacological action of fondaparinux

Introduction

Diabetes is a pro-inflammatory, pro-atherosclerotic and prothrombotic disorder. Diabetic patients suffering from acute coronary syndromes (ACS) are at a higher incidence of recurrent cardiovascular events and have a two-fold increase in both short- and long-term mortality compared to non-diabetic patients, independent of any other risk factors. Central to the management of these patients in the acute management of ACS is blockade of the prothrombotic state mediated by the coagulation cascade. Fondaparinux, an indirect inhibitor of factor Xa, has been shown to be advantageous in comparison to older agents such as enoxaparin and unfractionated heparin (UFH) in certain clinical settings. The use of fondaparinux in ACS has since been advocated in both national and international guidelines.

Pharmacology

Fondaparinux is a synthetic sulfated pentasaccharide, which acts as a selective indirect inhibitor of factor Xa. This process is mediated by the high affinity binding of fondaparinux to plasma antithrombin, which results in a 300-fold increase in the inhibition of factor Xa by antithrombin (Figure 1). This inhibition of factor Xa is irreversible; however, the interaction between fondaparinux and antithrombin is not, allowing each single molecule of fondaparinux to bind to and activate several molecules of antithrombin. Factor Xa sits at the convergence of the intrinsic and extrinsic coagulation pathways and under normal circumstances the activation of one molecule of factor X results in the production of 1000 molecules of thrombin. The antithrombin-mediated inhibition of the coagulation cascade through inactivation of factor Xa results in a reduction in thrombin generation and fibrin clot formation.

Fondaparinux is administered as a once-daily subcutaneous injection with a time to peak plasma concentration of around 2 hours and a half-life of 17 hours. It is excreted by the kidneys and is contraindicated in patients with an eGFR of <20ml/min/1.73m^2. It should also be noted that fondaparinux is not associated with heparin-induced thrombocytopenia and has been shown to be safe for prevention of thrombosis in affected patients. Patients prescribed fondaparinux

require no monitoring of their anticoagulant activity.

Trials of safety and efficacy

The most common surgical cause of thrombotic complications are major orthopaedic procedures, and fondaparinux has been intensively investigated in this setting. A meta-analysis of four large (7344 patients) double-blind randomised studies involving hip replacements, hip fractures and major knee surgery concluded that fondaparinux reduced the incidence of thromboembolism by 51% ($p<0.001$) in comparison to enoxaparin given at a dose of either 40mg once daily or 20mg twice daily.

The MATISSE trials examined fondaparinux in the setting of treatment of deep venous thrombosis versus enoxaparin, and in pulmonary embolus versus unfractionated heparin. In both trials, it was found that fondaparinux was non-inferior to the comparator with no statistically significant differences in bleeding events or mortality.

OASIS-5 recruited 20 078 patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina, and randomised them to either fondaparinux or enoxaparin at a dose of 1mg/kg twice daily with a maximum follow up of 180 days.[1] Fondaparinux (5.8%) was shown to be non-inferior to enoxaparin (5.7%) in the number of patients meeting the primary endpoint of death, myocardial infarction or refractory ischaemia up to day nine (HR 1.01; 95% CI 0.90–1.13). The rate of major bleeding at nine days in the fondaparinux group was significantly lower than enoxaparin (HR 0.52; $p<0.001$) and the composite of primary endpoint and bleeding at nine days was lower in the fondaparinux arm (7.3%) versus enoxaparin (9.0%) (HR 0.81; $p<0.001$). Fondaparinux was also associated with a reduction in mortality rate at both 30 (17%; $p=0.02$) and 180 days (11%; $p=0.05$).

OASIS-6 enrolled 12 092 patients with ST elevation myocardial infarction (STEMI) and randomised to either fondaparinux or standard therapy (placebo or unfractionated heparin when indicated).[2] In those patients randomised to fondaparinux, there was a 14% ($p=0.008$) reduction in the primary endpoint of death or reinfarction at 30 days. However, this benefit was not seen in those patients undergoing primary percutaneous coronary intervention (PCI) and, additionally, patients receiving fondaparinux had a higher rate of complication with catheter thrombosis. The greatest benefits in those patients receiving fondaparinux were seen in those receiving concomitant thrombolytic therapy (HR 0.79; $p=0.003$) and those not receiving any reperfusion therapy (HR 0.80; $p=0.03$). Patients receiving fondaparinux had a tendency to less severe bleeding events (HR 0.77; $p=0.13$).

Specific evidence for use in diabetes

A subgroup analysis of the diabetic population in the OASIS-5 cohort confirmed the superiority of fondaparinux over enoxaparin with a significantly reduced mortality at six months and reduced incidence of major bleeding events in both diabetic and non-diabetic subgroups.[3]

In OASIS-6, 17.8% of the cohort had diabetes. More diabetic patients versus non-diabetic patients (13.9% vs 8.8% in the fondaparinux arm, 14.2% vs 10.5% in the standard treatment arm) met the primary endpoint of death or reinfarction at 30 days.[4] In non-diabetic patients, fondaparinux was associated with a significantly reduced incidence of the primary endpoint (HR 0.83, 95% CI 0.73–0.94). Fondaparinux was at least as effective as standard treatment in diabetic patients and was associated with a two-fold reduction in severe bleeding events in comparison to standard treatment (0.7% vs 1.7%) in the diabetic population; however, the event rate was very low. The authors of the subgroup analysis concluded that, in diabetic patients with ST elevation myocardial infarction, fondaparinux offered a greater benefit–risk ratio than standard treatment.

Discussion

Blockade of the coagulation cascade in ACS reduces the risk of further thrombosis and recurrent myocardial ischaemia. This is of importance in diabetic patients who have a higher rate of recurrent cardiovascular events. Although beneficial in terms of reduction of risk of thrombosis, anticoagulation therapy is associated with an increased risk of bleeding and choice of therapy must be made in terms of the greatest efficacy-safety profile. In the setting of NSTEMI, on the basis of the results seen in the OASIS-5 trial, the use of fondaparinux at a dose of 2.5mg is the recommended choice of anticoagulant in both national (SIGN, NICE) and international (European Society of Cardiology, ESC) guidelines. Fondaparinux was found to be non-inferior to enoxaparin in the number of patients reaching the trial's primary endpoint; however, it was associated with a significantly lower incidence of major bleeding events and conferred a benefit in mortality at both 30 and 180 days. OASIS-6, in the setting of STEMI, found that fondaparinux demonstrated a significant benefit in mortality and incidence of reinfarction in comparison to UFH or placebo. This benefit was not seen in those patients undergoing primary PCI but was evident in those undergoing thrombolysis or no form of reperfusion therapy. Given these results, fondaparinux is recommended in ESC guidelines for those STEMI patients who are undergoing thrombolysis or no reperfusion therapy but not those having primary PCI.

Key points

- Fondaparinux, an indirect factor Xa inhibitor, is an effective anticoagulant agent with a simple, once-daily, fixed dosing regimen of 2.5mg with no monitoring requirement
- Fondaparinux has shown to be beneficial compared to enoxaparin in diabetic patients with NSTEMI and unstable angina with a reduction in mortality and bleeding rates
- In the setting of STEMI, fondaparinux has been shown to be beneficial in diabetic patients undergoing thrombolysis or no perfusion therapy, but not those undergoing primary PCI

Declaration of interests

There are no conflicts of interest declared.

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References are available at www.practicaldiabetes.com.

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