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Review Article

Fondaparinux – data on efficacy and safety in special situations

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ABSTRACT

New anticoagulants promise to have better efficacy, more safety and/or a better manageability than traditional anticoagulants. However, knowledge is limited regarding special situations such as renal insufficiency, obesity, pregnancy, long-term therapy, heparin-induced thrombocytopenia, treatment in patients with mechanical heart valves, use for children, and in patients with a high risk of thromboembolic complications. These situations have rarely or even never been the objective of randomised controlled trials. The purpose of the present article is to summarize and discuss available data on efficacy and safety in these special situations for one of the first new anticoagulants, the indirect factor-Xa inhibitor fondaparinux. Furthermore, we discuss safety in licensed indications and management of bleeding complications and comment on measuring of drug concentration in plasma.

Contents

Abbreviations: ACS, acute coronary syndrome; anti-Xa, anti-factor Xa activity; APS, antiphospholipid syndrome; BID, twice a day; BMI, body mass index; DVT, deep vein thrombosis; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FEIBA, factor eight inhibitor bypassing activity; FFP, fresh frozen plasma; GFR, glomerular filtration rate; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MDRD, Modification of Diet in Renal Disease formula; OD, once daily; PCC, prothrombin complex concentrate; PE, pulmonary embolism; PF4, platelet factor 4; rFVIIa, recombinant factor VIIa; s.c., subcutaneously; SRA, serotonin release assay; SVT, superficial vein thrombosis; Swissmedic, Swiss Agency for Therapeutic Products; UFH, unfractionated heparin; VKA, vitamin K antagonists; VTE, venous thromboembolism.

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Introduction

Despite recent advances in anticoagulation therapy there are regularly situations in clinical practice, which are not covered by current guidelines [1–4]. These include renal insufficiency, obesity, pregnancy, use for children, heparin-induced thrombocytopenia, and long-term therapy e.g. in patients with mechanical heart valves and in patients with a high risk of thromboembolic complications, particularly if vitamin K antagonists (VKA) and/or heparin derivatives are inappropriate. These situations have rarely or even never been the objective of randomised controlled trials. Problems with VKA therapy can include bleeding complications, inability to achieve the target international normalised ratio (INR), venous thromboembolism in spite of adequate anticoagulation or rare situations such as the presence of a factor IX propeptid mutation. Furthermore, there are non-bleeding side effects such as hair loss, fatigue, or elevations of hepatic enzymes. Possible problems with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) are heparin-induced thrombocytopenia (HIT), hypersensitive skin reactions or failure of absorption. New anticoagulants promise to have better efficacy, more safety and/or a better manageability than traditional anticoagulants. However, knowledge is limited regarding special situations.

The purpose of the present article is to summarize and discuss available data on efficacy and safety in these special situations for one of the first new anticoagulants, the indirect factor-Xa inhibitor fondaparinux. Furthermore, we discuss safety in licensed indications and management of bleeding complications and comment on measuring of drug concentration in plasma.

Mechanism of action and pharmacokinetics

Fondaparinux is a pentasaccharide which strongly binds to antithrombin and enhances the inactivation of factor Xa without interaction with factor II or platelets [5]. It has a markedly increased affinity for antithrombin and improved inhibition of thrombin generation in comparison with UFH [6]. Furthermore, in an animal model it shows a stronger anticoagulation effect in arterial thrombosis [7]. Fondaparinux has a high bioavailability (107%; 90% CI 102 – 112%) two hours after subcutaneous (s.c.) administration and an elimination half-life of 17 to 21 hours [8,9]. This enables once-daily dosing. Unmetabolized excretion through the kidneys warrants caution in patients with impaired renal function. Very low intra- and intersubject variability [9] makes drug monitoring and dose adjustments in most cases unnecessary. There were no relevant drug interactions in corresponding investigations and in phase III clinical trials [10–12]. Data on pharmacokinetics are summarized in Table 1.

Safety of fondaparinux in recommended indications

Recommended indications of fondaparinux are summarized in Table 2. Fondaparinux 2.5 mg is recommended for the prevention of VTE in major orthopaedic surgery, major abdominal surgery and medical patients [2]. In phase III clinical trials, it did show superior efficacy or non-inferiority compared to enoxaparin, UFH or physical measures alone [13–17]. Although prevention trials did show a slight increase in major bleeding events, this was counterbalanced by a consistent pattern in reduced mortality [18]. Although statistically not significant, the effect of reduced mortality was internally consistent, as it was seen in nearly all subgroups and externally consistent as it was observed in all trials. In addition, most of the bleeding complications occurred if fondaparinux was given within 6 hours after surgery [13,19]. If administered at a correct interval after interventions (6 to 8 hours), ACCP guidelines consider prophylaxis with fondaparinux 2.5 mg as safe as a prophylactic dose of LMWH or UFH [20]. To enhance feasibility of postoperative application, a delayed initiation of fondaparinux treatment (morning after surgery) was tested and proved to have comparable efficacy in preventing thrombembolic complications [21]. Another important safety concern is when continuous neuraxial or deep peripheral nerve catheters are used postoperatively. In phase III clinical trials type of anaesthesia was left to the discretion of the anaesthesiologist and 30 – 65% of the patients received regional anaesthesia [22]. No case of spinal or epidural haematoma was observed, however [15,17,23–26]. A prospective cohort study investigated efficacy of fondaparinux treatment if application was discontinued for 48 hours to allow removal of neuraxial or peripheral nerve catheter (n = 1431). Catheter was removed 36 hours after last application and 12 hours before next application with a comparable efficacy and safety in patients with and without a catheter (and discontinuation of fondaparinux) [27].

A recent study of fondaparinux 2.5 mg vs. placebo for treatment of superficial vein thrombosis (SVT) showed efficacy in terms of prevention of deep vein thrombosis (DVT) respective pulmonary embolism (PE) without any increase in major bleeding [28].

Fondaparinux 7.5 mg is recommended as initial treatment of DVT and PE because of its comparable efficacy to LMWH (DVT) or UFH (PE) [3,29,30]. In both phase III studies, bleeding complications were similar to the comparator. For that reason, ACCP guidelines consider therapeutic doses of fondaparinux (7.5 mg, respectively 10 mg in case of body weight >100 kg and 5 mg if <50 kg) comparable safe to therapeutic doses of UFH/LMWH [20].

Fondaparinux 2.5 mg is recommended for the treatment of acute coronary syndrome (ACS) by ACCP, ACC-AHA and ESC [12,31–33]. Phase III clinical trials showed efficacy comparable or superior to LMWH/UFH in respect of myocardial infarction as well as a significant reduction in mortality at most of the points in time [34,35]. Furthermore, a reduction in major bleeding events was observed compared to enoxaparin, most markedly in the case of non-ST elevation ACS at day 9 (Hazard ratio 0.52; 95% CI 0.44 – 0.61). Therefore, fondaparinux is particularly recommended for patients at high risk of bleeding complications such as the elderly, women, patients with renal impairments and those with anaemia [32,33]. Because of a trend towards higher mortality in a subgroup of patients, fondaparinux only carries a 1B recommendation and is not recommended in cases of primary angioplasty [36].

Table 1
Mechanism of action and pharmacokinetics of fondaparinux.

Mechanism of action	Binding to antithrombin with high affinity. Inactivation of factor Xa
Bioavailability	100%, two hours after s.c. application
Elimination half-life	17 to 21 hours(young healthy volunteers - elderly)
Elimination	Excreted unmetabolized in urine (80%)
Metabolism	Not demonstrated
Within-subject variability	Low (4.4 – 5.5%)
Inter-subject variability	Low (11.6 – 17.5%)
Interaction with digoxin	None
Interaction with aspirin	None
Batch-to-batch variability	None