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Fondaparinux, a Synthetic Pentasaccharide: The First in a New Class of Antithrombotic Agents — The Selective Factor Xa Inhibitors

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ABSTRACT

Despite currently available antithrombotic therapies, venous thromboembolism (VTE) remains a major cause of morbidity and mortality. Fondaparinux sodium (pentasaccharide), the first in a new class of antithrombotic agents developed for the prevention and treatment of VTE, inhibits thrombin generation by selectively inhibiting factor Xa. Fondaparinux exhibits complete bioavailability by the subcutaneous route and is rapidly absorbed, reaching its maximum concentration approximately 2 h post dosing. It has a terminal half-life of 13 to 21 h, permitting once-daily dosing. Fondaparinux's reproducible linear pharmacokinetic profile exhibits minimal intrasubject and intersubject variability, suggesting that individual dose adjustments will not be required for the vast majority of the population and that there will be no need for routine hemostatic monitoring. At therapeutic concentrations (<2 mg/L), fondaparinux exhibits >94% binding to its target protein, antithrombin. Within this same concentration range there is no specific binding by fondaparinux to plasma proteins commonly involved in drug binding, indicating a low potential for drug-drug interactions by protein displacement. Unlike antithrombotic agents prepared from animal extracts (heparins), fondaparinux is chemically synthesized; this leads to batch-to-batch consistency and the absence of potential risk of contamination

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problems. In recently completed phase III clinical trials in VTE prevention in major orthopedic surgery, fondaparinux showed significant superiority over the low-molecular-weight heparin enoxaparin, providing an overall >50% ($P < 0.001$) reduction in VTE risk without increasing clinically important bleeding. Additional clinical data support its potential benefits in other venous and arterial thrombotic disorders. In view of these collective findings, fondaparinux is expected to play a major role in the prevention and treatment of venous and arterial thrombotic disease.

INTRODUCTION

Venous thromboembolic disease (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism, is a major cause of morbidity and mortality (4,54). Currently available pharmacologic agents for the prevention and treatment of VTE include the oral anticoagulants and the heparins (28,29). These classes of antithrombotic agents have multiple coagulation cascade targets. Their use for the prophylaxis or treatment of VTE is often associated with a variable anticoagulant response and a range of undesirable side effects. Recently, newer antithrombotic agents have been developed based on a single targeted approach where individual components of the coagulation cascade are selectively inhibited. These drugs may offer improved efficacy and safety over existing VTE therapies (76). This review focuses on the biologic and pharmacologic properties and the clinical performance of the novel antithrombotic agent fondaparinux (pentasaccharide; SR90107A/Org31540, Arixtra®), placing it in the context of current VTE therapies.

CURRENT ANTITHROMBOTIC AGENTS FOR VTE PREVENTION AND TREATMENT

The main antithrombotic agents currently used for VTE prevention and treatment are oral anticoagulants (vitamin K antagonists) and the heparins, including unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs). Relatively newer agents such as the heparinoids and direct thrombin inhibitors (DTIs) have more limited use.

Oral vitamin K antagonists (e.g., warfarin) interfere with the synthesis of vitamin K-dependent, Gla (γ-carboxyglutamic acid) domain-containing proteins. This includes many of the zymogens of the coagulation cascade (factors II, VII, IX, X) as well as the regulatory anticoagulant proteins, protein C and protein S (57). Genetic and environmental factors affect the dose-response relationship of oral anticoagulant therapy necessitating frequent laboratory monitoring of hemostatic parameters to achieve target international normalized ratios (INRs) (27). This need for frequent monitoring to insure that INRs are not above or below the target therapeutic range — which would predispose to bleeding or thrombotic complications, respectively — complicates the clinical use of oral anticoagulant therapy.

UFH is the commercially isolated, therapeutic derivative of the natural anticoagulant molecules, heparan sulfates, that line the endothelium and contribute to its anticoagulant properties (51). UFH preparations consist of a heterogeneous mixture of polymers that range in molecular weight from 3000 to 30,000 Da, with an average molecular weight of approximately 15,000 Da (5). Only about 30% of the molecules in UFH exhibit anticoagulant activity (35). The main pharmacological effects of UFH are anti-factor IIa

(thrombin) and anti-factor Xa activities, although factors IXa, and, to some degree, XIa and XIIa are also inhibited (49).

UFH binds nonspecifically to plasma and cellular proteins. This nonspecific protein binding reduces the therapeutic bioavailability of UFH and results in wide variability in its antithrombotic dose response. Thus, the use of UFH requires frequent laboratory monitoring to achieve the desired antithrombotic effect while minimizing the risk of bleeding (13). The binding of UFH to platelets can interfere with platelet aggregation (40), potentially promoting bleeding complications. The clinical use of UFH is further limited by the associated risk of heparin-induced thrombocytopenia (HIT). UFH binding to platelet factor 4 (PF4) results in a highly immunogenic complex that can lead to the generation of anti–heparin-PF4 antibodies. The binding of these antibodies to the platelet surface stimulates platelet aggregation, which may lead to the potentially life-threatening thrombotic complications that are the hallmark of clinical HIT (74). Finally, UFH stimulates osteoclast activation, which can result in osteoporosis (39).

LMWHs are produced from UFH by chemical or enzymatic cleavage followed by fractionation to isolate the low-molecular-weight derivatives formed. Similar to UFH, LMWHs are structurally heterogeneous, containing molecules that range from 1000 to 10,000 Da, with an average molecular weight of 4500 to 5000 Da (29). LMWHs have a 2- to 4-fold greater effect on factor Xa than on thrombin. LMWHs have a longer half-life, better bioavailability, and a more predictable dose response than UFH, obviating the need for frequent laboratory monitoring (24). Compared with UFH, LMWH therapy is less frequently associated with clinical HIT (75). In view of pre-clinical data suggesting improved efficacy and safety of LMWHs, many believed that the use of LMWH for the prevention and treatment of VTE might lead to fewer bleeding complications compared with UFH therapy. However, clinical trials are inconclusive in this regard, with many failing to show any reductions in bleeding complications or decreased rates of recurrent thrombosis (15,23). Thus, LMWHs represent a superior form of antithrombotic therapy, relative to UFH, primarily in terms of pharmacologic profile and ease of use.

Heparinoids, such as danaparoid, are mixtures of natural glycosaminoglycans (1). Danaparoid has been shown to be as safe and effective for reducing the recurrence or extension of VTE (14) but, for the most part, the use of danaparoid has been limited to the treatment of thrombosis in patients with HIT (74). Other antithrombotic agents useful for the treatment of HIT include the DTIs such as lepirudin and argatroban, the only US Food and Drug Administration (FDA) approved agents for this indication. Although, DTIs, as a class of antithrombotic agents, are used less frequently than heparins, they do offer several potential advantages. These advantages include a lack of structural similarity to heparin and reactivity with PF4, and the ability to inhibit thrombin bound to fibrin or fibrin degradation products (76). DTIs such as ximelagatran are under development and will offer the convenience of oral dosing (21) provided that efficacy and safety are achieved without the need for laboratory monitoring.

SELECTIVE FACTOR Xa INHIBITORS

Factor Xa is critically positioned at the junction of the extrinsic and intrinsic pathways of the coagulation cascade, and thus its inactivation substantially inhibits thrombin generation regardless of the initiating pathway. Factor Xa inhibition is an efficient mechanism

for indirectly limiting thrombin activity since inactivation of one molecule of factor Xa inhibits the generation of many molecules of thrombin (77).

Selective Direct Factor Xa Inhibitors

A number of direct factor Xa inhibitors are under development, including synthetic molecules such as DX-9065a (41) and YM-60828 (53). In addition, naturally occurring inhibitors originally isolated from leeches or ticks but now produced by recombinant techniques such as antistasin (62) and tick anticoagulant peptide (67), are also under development. These inhibitors bind directly to the catalytic site of factor Xa. Some of these direct factor Xa inhibitors, because of their relatively small size, are able to inhibit factor Xa bound to the prothrombinase complex or to fibrin, in addition to inhibiting free factor Xa. Whether this feature represents an important advantage in terms of limiting thrombosis, or a disadvantage because of the potential for inducing bleeding complications at an increased rate, remains, at present, theoretical. These agents are either in preclinical or relatively early stages of development (76).

Selective Indirect Factor Xa Inhibitors

Fondaparinux sodium is the first in a new class of selective, indirect factor Xa inhibitors (10). It is an antithrombin (AT; formerly referred to as antithrombin III)-mediated factor Xa inhibitor that is devoid of any anti-factor IIa (thrombin) activity. It acts as a catalyst for AT, the primary endogenous inhibitor of the coagulation cascade, resulting in an approximate 300-fold acceleration in its basal rate of factor Xa inactivation (42) with no effect whatsoever on its basal rate of thrombin inactivation. Fondaparinux is a small, synthetically produced molecule; it is a single entity and preparations are structurally homogeneous and consistent from batch to batch.

FONDAPARINUX: AN UPDATE OF ITS BIOLOGIC AND PHARMACOLOGIC PROPERTIES

Two reviews describing the development and characterization of the synthetic pentasaccharide, fondaparinux, were published in 1997 (26,71). Much has been learned since then and these findings are emphasized here, following a brief summary of the molecule's development.

The history of the synthetic pentasaccharide (SR90107A/Org31540, fondaparinux sodium) is reflected in the various names by which this molecule has been referred to since the synthesis, in 1983, of a closely related pentasaccharide that represented the AT binding region of heparin (10). An appreciation for the role of heparin in potentiating the natural anticoagulant activity of AT (50) led to an effort to isolate and characterize the sequence within unfractionated heparin capable of generating this activity. Studies by Choay and coworkers identified a natural, biologically active hexasaccharide within digests of enzymatically treated heparin and suggested that a specific pentasaccharide sequence contained within the hexasaccharide would also be likely to retain high anti-factor Xa activity (9). Synthesis of a slightly modified, 1714-Da, "original pentasaccharide", as the molecule was referred to, was first reported by Choay, Sinay, Petitou, and coworkers (10,46,56).

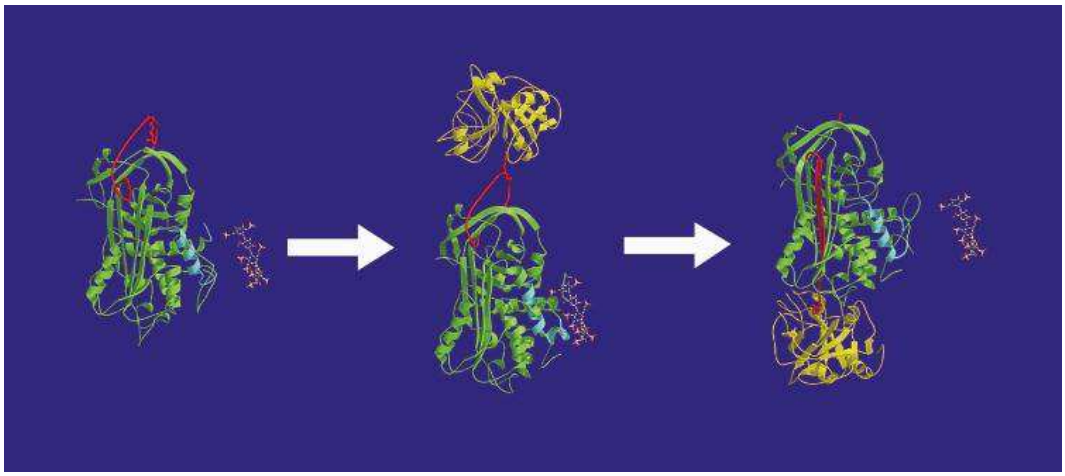

FIG. 1. Fondaparinux mechanism of action: Specific inhibition of factor Xa via antithrombin III (AT). Left: Fondaparinux approaches the AT molecule. Middle: The binding of fondaparinux induces a conformational change in AT that greatly enhances the affinity of AT for factor Xa. Right: AT binds to factor Xa, releasing fondaparinux, which can then bind to another AT molecule. Figure kindly provided by Carrell R, Huntington J. Hematology Department, Cambridge University, 2000.

Subsequently, van Boeckel, Ichikawa, and coworkers reported alternate synthetic approaches for the pentasaccharide that offered improved efficiency (31,66). The critical role, for AT binding, of selected sulfate and carboxylate residues within the pentasaccharide sequence was identified by these same groups (6,45,47,63,65,73). To insure chemical stability and improve synthetic yield, the synthesis of α-methyl derivatives of the pentasaccharide was performed (44). From a series of such α-methyl derivatives (65) the "stabilized", 1728-Da, synthetic pentasaccharide was selected for development. Originally referred to as SR90107A/ORG31540, it is now known as fondaparinux sodium.

Biophysical Characterization of Pentasaccharide-Enhanced AT Activity

Biochemical and biophysical studies have suggested that the binding of pentasaccharide to AT induces a conformational change that enhances exposure of the reactive loop involved in AT's inactivation of factor Xa (42). Using molecular modeling, a detailed mechanism for this activation has been proposed (64). Fondaparinux has been co-crystallized with AT. It binds to the serpin in the same way as previously reported for a close analogue that was also co-crystallized with AT (32). These collective findings are consistent with the concept of a catalytic role for pentasaccharide in dramatically enhancing the rate of AT-mediated factor Xa inactivation. In this process, pentasaccharide binds with high affinity, but reversibly, to AT. It is not consumed in the inactivation of factor Xa but, rather, is released from AT once the serpin has bound to its target protease (Fig. 1). Its renewed availability, therefore, contrasts sharply with the mechanism of action of the direct factor Xa inhibitors. The extent to which this distinction does, or does not, translate into clinical advantage remains unclear at present since none of the direct factor Xa inhibitors has yet been evaluated in advanced clinical trials.

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