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Review Article

The mechanism of action of rivaroxaban – an oral, direct Factor Xa inhibitor – compared with other anticoagulants

Meyer Michel Samama *

Hôtel-Dieu University Hospital, Paris, France
Biomnis Laboratories R&D, Ivry-sur-Seine, France

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ABSTRACT

Although results of some phase III clinical trials of new oral anticoagulants are now known, it is important to understand the mechanisms of their actions. These new agents exert their anticoagulant effect via direct inhibition of a single Factor within the coagulation cascade (such as Factor Xa or thrombin). Rivaroxaban – the first oral, direct Factor Xa inhibitor – is a small-molecule oxazolidinone derivative that binds directly and reversibly to Factor Xa via the S1 and S4 pockets. Rivaroxaban competitively inhibits Factor Xa and is more than 10,000-fold more selective for Factor Xa than other related serine proteases, and it does not require cofactors (such as antithrombin) to exert its anticoagulant effect. Unlike indirect Factor Xa inhibitors, rivaroxaban inhibits both free and clot-bound Factor Xa, as well as prothrombinase activity, thereby prolonging clotting times. Dabigatran etexilate is a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Although the mechanism of action differs between the direct Factor Xa and direct thrombin inhibitors, phase III studies of these new agents confirmed that both Factor Xa and thrombin are viable anticoagulation targets.

Contents

Abbreviations: ACS, acute coronary syndrome; aPTT, activated partial thromboplastin time; AT, antithrombin; AUC, area under the curve; bid, twice daily; C_{max}, maximum plasma concentration; CrCl, creatinine clearance; CYP, cytochrome P450; IC_{50}, inhibitory concentration 50; INR, international normalized ratio; LMWHs, low molecular weight heparins; od, once daily; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PT, prothrombin time; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TG, thrombin generation; THR, total hip replacement; TKR, total knee replacement; UFH, unfractionated heparin; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

* Biomnis Laboratories R&D, 78 avenue de Verdun, BP 110, 94200 Ivry-sur-Seine cedex, France. Tel.: +33 1 49 59 16 02; fax: +33 1 49 59 15 29.
E-mail address: meyermichel.samama@biomnis.com.

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Introduction

Thromboembolic disorders are major causes of morbidity and mortality. Arterial thrombosis is the most common cause of myocardial infarction and ischaemic stroke, whereas deep vein thrombosis can lead to pulmonary embolism [1]. In the USA, pulmonary embolism causes almost 300,000 deaths per annum [2]. It is estimated that 12% of the annual deaths occurring in France, Germany, Italy, Spain, Sweden and the UK are due to venous thromboembolism (VTE), varying from 10% in the UK to 14% in Italy [3].

Great advances have been made in understanding the molecular and cellular basis of thrombus formation in the past few decades, with anticoagulants remaining the cornerstone for the prevention and treatment of thromboembolic disorders [4–6]. Conventional anticoagulant therapies, such as unfractionated heparin (UFH), low molecular weight heparins (LMWHs) and vitamin K antagonists (VKAs), act on multiple factors within the coagulation cascade. The heparins exert their anticoagulant effect by binding to antithrombin (AT) via a pentasaccharide sequence and increasing the ability of AT to inhibit Factor Xa and thrombin and other factors [7]. The anticoagulant effect of the VKAs is achieved by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide, leading to the hepatic production of partially carboxylated and decarboxylated coagulation factors (VII, IX, X and II) with reduced coagulant activity [8]. Although effective, these traditional agents are associated with several drawbacks, including parenteral route of administration or routine coagulation monitoring and dose adjustments. Recent efforts in finding new approaches to anticoagulation have focused on targeting a single enzyme within the coagulation pathway, such as thrombin and Factor Xa, and inhibition of either of these coagulation enzymes attenuates fibrin formation.

Factor Xa has emerged as a promising target for effective anticoagulation because it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways. Several new oral agents that specifically target Factor Xa have been developed, and rivaroxaban is one of the agents in late-stage clinical development. This article will give an overview of the oral, direct Factor Xa inhibitor rivaroxaban, comparing it with the indirect Factor Xa inhibitor (fondaparinux), other direct Factor Xa inhibitors (apixaban and edoxaban), and the direct thrombin inhibitor dabigatran etexilate. The potential advantages of direct Factor Xa inhibition will also be discussed.

The coagulation pathway

Tissue factor (TF) is the sole initiator of thrombin generation (TG) and fibrin formation [9]. Under normal conditions, the endothelium acts as a barrier separating TF from Factor VIIa in flowing blood. However, TF is also present in circulating blood, and this blood-borne TF plays an important role in the initiation of coagulation when vessel injury is limited to endothelial activation [9]. TF binds to circulation Factor VIIa to form the TF–Factor VIIa complex, which activates Factor IX and Factor X (Fig. 1). Tissue factor pathway inhibitor (TFPI) is an important physiological inhibitor of Factor Xa at the initial phase of blood coagulation. It binds to Factor Xa and blocks the TF–Factor VIIa–Factor Xa complex [10]. Recent evidence suggests that TFPI also plays a role in the protein S pathway; TG is increased when TFPI is inhibited [11]. It should be noted that TFPI is present in a low concentration (~2.5 nmol/l) in blood [10]. The anticoagulant role of TFPI in combination with that of Factor Xa inhibition requires further attention. Factor Xa converts small amounts of prothrombin to thrombin. Thrombin then amplifies coagulation by activating Factor V and Factor VIII (on the surface of activated platelets), platelets and platelet-bound Factor XI. The coagulation cascade is amplified by further generation of Factor Xa by the Factor IXa–Factor VIIIa–Ca^{2+}–phospholipid complex. Factor Xa binds to negatively charged phopholipid surfaces (e.g. activated platelets), together with Factor Va to form the prothrombinase complex – the central prothrombin activator, which converts prothrombin to thrombin [12]. Thrombin plays a central role in the clotting process. In addition to converting soluble fibrinogen to fibrin and activating platelets, thrombin also amplifies its own generation by feedback activation of Factor VIII and Factor V, as well as activating Factor XIII, which further stabilizes the clot. The coagulation pathway is regulated by natural anticoagulants, such as the TF pathway inhibitor, AT and the protein C and protein S system [13].

Indirect Factor Xa inhibitor

Fondaparinux

Fondaparinux is a synthetic analogue of the AT-binding pentasaccharide found in UFH or in the LMWHs. Its molecular weight (1728 g/mol) is approximately three times lower than that of LMWHs. It exerts its anticoagulant effects by binding to AT and evoking a conformational change at the reactive site of AT, which enhances its reactivity with Factor Xa [14]. Because it is too short to bridge AT to thrombin, fondaparinux does not increase the rate of thrombin inhibition by AT [15]. Fondaparinux produces a predictable anticoagulant response that precludes the need for routine coagulation monitoring and does not cause heparin-induced thrombocytopenia [15]. Unlike the direct Factor Xa inhibitors or direct thrombin inhibitors, fondaparinux does not prolong prothrombin time (PT) and has a very weak effect on the activated partial thromboplastin time (aPTT) [16]. However, as with the LMWHs, fondaparinux must be administered subcutaneously (Table 1).

Direct Factor Xa inhibitors

Rivaroxaban

Rivaroxaban is an oral, direct Factor Xa inhibitor. The onset of inhibition of Factor Xa activity with rivaroxaban is rapid and the inhibition is reversible. The values for k_{on} and k_{off} are 1.7×10^7 M^{-1} s^{-1} and 5×10^{-3} s^{-1}, respectively [17]. It is a small molecule (Mr 435.9 g/mol) and it binds directly to the active site of Factor Xa via the S1 and S4 pockets (Fig. 2) [18].

The X-ray crystal structure of rivaroxaban in complex with human Factor Xa clarified the binding mode and the requirements for high

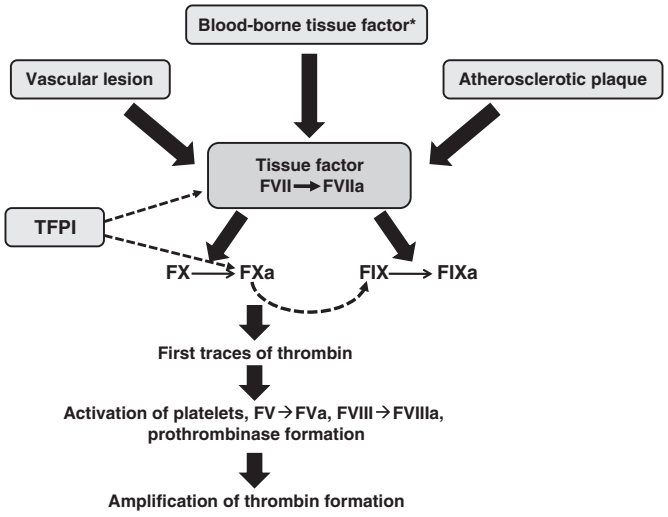

Fig. 1. Schematic representation of the coagulation cascade. Tissue factor pathway inhibitor (TFPI) binds to FXa, then the complex TFPI–FXa binds to tissue factor–FVIIa forming an inactive quaternary complex. *Activated monocytes/macrophages. FV, Factor V; FVa, activated Factor V; FVII, Factor VII; FVIIa, activated Factor VII; FVIII, Factor VIII; FVIIIa, activated Factor VIII; FIX, Factor IX; FIXa, activated Factor IX; FX, Factor X; FXa, activated Factor X.