Rivaroxaban: Mechanism of Action and Target Protein Factor Xa

Poster Team: T. Chaney, M. Duffy, C. May, M. Robinson, C. Rodenkirch, A. Thurmer
Jmol Team: A. Glueckstein, K. Kim
Faculty Advisor: Daniel Sem, Ph.D.
Concordia University of Wisconsin School of Pharmacy
Professional Mentors: Eleanor Shterenfeld, PharmD and Mike Gillard, PharmD

Abstract

In 2011, the FDA approved rivaroxaban for prophylaxis of deep vein thrombosis (DVT) in adults undergoing hip and knee replacement surgery to reduce the 40-60% risk of DVT[1]. Rivaroxaban, a direct thrombin inhibitor, blocks FXa in the thrombin pathway reducing the possibility of clot formation leading to a venous thromboembolism[2]. The venous thromboembolism practice guidelines state that rivaroxaban should be started 6 hours after surgery for prophylaxis in total hip replacement procedures[1].

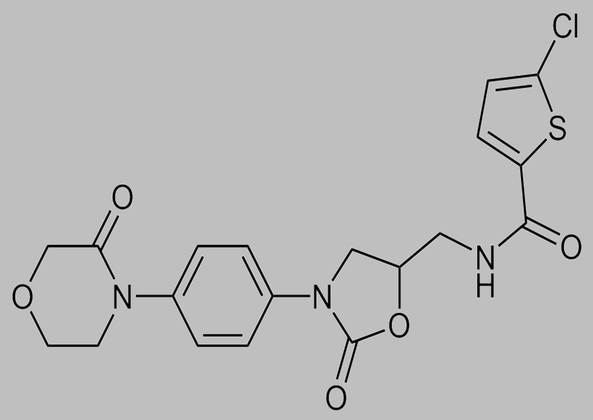

Fig. 1- Rivaroxaban molecular structure
http://commons.wikimedia.org/wiki/File:Rivaroxaban.png

Introduction

A 65 year old female presented with a proximal femoral fracture, requiring hip replacement, as the result of a car accident. Her past medical history included knee replacement three years prior. Due to high risk of deep vein thrombosis (DVT), rivaroxaban (Xarelto) was considered for pre/post-surgical therapy.

This fairly new oral anticoagulant reduces DVT risk by binding to both free and complex Factor Xa (FXa)[3]. It is highly selective at blocking prothrombinase complex since FXa is the central point in the coagulation cascade. Studies have shown it to be statistically significant in DVT prophylaxis post-orthopedic surgery[2]. The burden of rivaroxaban is lower than other options due to its oral bioavailability.

At this time, no daily or routine monitoring is necessary for this anticoagulant and it may be taken with or without food. A major adverse side effect with this medication is the risk for bleeding. Strong CYP3A4 and P-glycoprotein inhibitors such as ketoconazole, itraconazole, voriconazole, posaconazole, and ritonavir should be avoided when using rivaroxaban. With this knowledge, the healthcare team decided to start the patient on rivaroxaban.

Molecular Story

Fig. 2- Coagulation Factor Xa.
Image rendered from 2W26.pdb

Rivaroxaban interacts with FXa in two major binding pockets, the S1 pocket and the S4 pocket[4].

In addition, Gly219 forms two hydrogen bonds with the drug's oxazolidinone core[4].

These hydrogen bonds give rivaroxaban its bent, L type shape. This L shape was designed to have the oxazolidinone core structure direct the morpholinone residue into the S4 pocket and the chlorthiophene moiety into the S1 pocket[4].

Figure 5. Ribbon structure of FXa showing bound Rivaroxaban. Rendered from 2W26.pdb

Factor Xa, also known as prothrombinase, is an enzyme involved in the main coagulation cascade after endothelial injury[4].

FXa converts prothrombin to thrombin by cleaving specific peptide bonds, arginine-threonine and arginine-isoleucine, yielding activated thrombin[4].

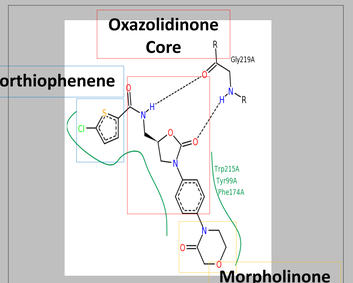

Figure 3. The three main components of Rivaroxaban. Rendered from 2W26.pdb

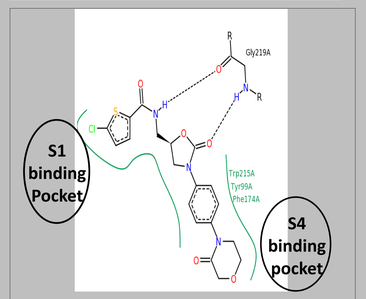

Figure 4. The approximate binding pocket areas, S1 and S4. Rendered from 2W26.pdb

Within the S1 pocket, the chlorine atom of rivaroxaban interacts with the aromatic ring of Tyr228[4].

This key interaction results in high affinity with FXa without a basic or positively charged group[4].

With this high affinity in a nonbasic compound, good oral bioavailability and high potency is achieved with rivaroxaban[4].

Improvements to Drug Design

Currently, there is no known mechanism for the reversal of rivaroxaban's effects. This poses a problem for those patients at greater risk for bleeds. One possible way to counteract this danger is to add biotin to rivaroxaban. This biotin molecule could be added to a carbonyl of the morphilinone moiety. This binding site is preferable because it has no interaction with FXa.

Biotin could be used to reverse the effects of rivaroxaban because it irreversibly binds to Avidin. Avidin is a high affinity biotin-binding protein. Together, this complex forms the strongest non-covalent interaction. Once Avidin is bound to biotin, it is thought to negatively impact the structure-activity relationship of biotin and its constituents (in this case, rivaroxaban)[5].

With this new addition to rivaroxaban, it is possible that the adverse effect of bleeding could be reversed.

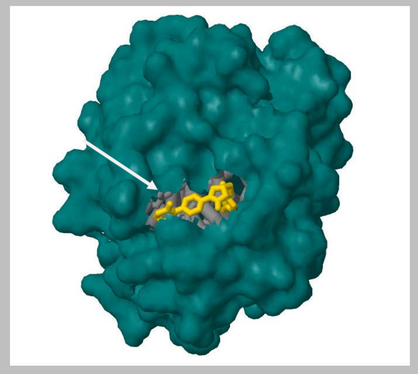

Figure 6. Arrow points to non-interacting carbonyl group of Rivaroxaban.
Rendered from 2W26.pdb.

Summary

Rivaroxaban has been proven in multiple studies to be superior to other standard anticoagulants when used for venous thrombosis prophylaxis post hip/knee surgery. It has a high affinity for FXa, therefore decreasing the conversion of prothrombin to thrombin. This inhibition prevents normal clotting processes from occurring.

References

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