Apixaban : Selective Inhibitor of Factor Xa in the Coagulation Cascade

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Abstract

Apixaban (Eliquis) is a novel anticoagulant used in the prevention of blood clot formation. Specifically, it is a selective inhibitor of factor Xa in the coagulation cascade, which is necessary for the conversion of prothrombin to thrombin. Apixaban is an organic, heterocyclic compound with a phenylpiperidine skeleton. The Lipinski's Rule of Five predicts apixaban is more membrane permeable and therefore more easily absorbed by the body within three to four hours of oral administration. Apixaban has a low volume of distribution suggesting it stays in the main blood compartment, where factor Xa is found. It is metabolized mainly by the CYP3A4 enzyme and eliminated via hepatic metabolism, renal excretion, and gastrointestinal/bile secretion. If used concomitantly with a CYP3A4 inhibitor, antiplatelet, or anticoagulant drug, excessive bleeding may occur, in which there are no reversal agents for. However, apixaban still remains a great secondary option for anticoagulant therapy as it does not require intense monitoring and has great oral bioavailability.

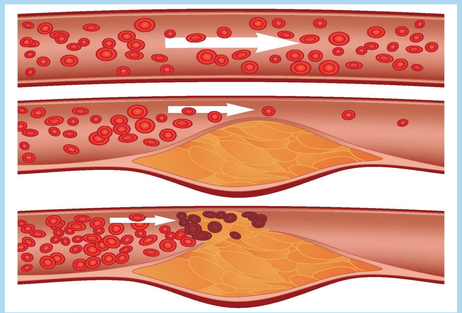

Fig. 1 Atherosclerosis and Blood Clot Formation
https://neuroendoimmune.files.wordpress.com/2014/02/clogged-artery.jpg

Introduction

- Apixaban (Eliquis) is a new novel anticoagulant
- Indications:
  - Deep Vein Thrombosis (DVT)
  - Pulmonary Embolism (PE)
  - Atrial Fibrillation
  - Prophylactic Risk Reduction Recurrence
- Selectively and directly inhibits factor Xa in the coagulation cascade to prevent fibrin clot formation
  - Blocks the conversion from prothrombin to thrombin
- Metabolized to inactive molecules by the liver via CYP450 enzymes, primarily CYP3A4
- Drug-to-drug interactions with:
  - CYP450 Inducers
  - CYP450 Inhibitors
  - Antiplatelets
  - Anticoagulants
- While on rotation, patient taking apixaban was at risk of experiencing drug-to-drug interactions with:
  - Ibuprofen (Antiplatelet)
  - Fluovoxamine (CYP450 inhibitor)
- Monitoring parameters:
  - Signs and symptoms of bleeding
  - Excessive bleeding

Molecular Story

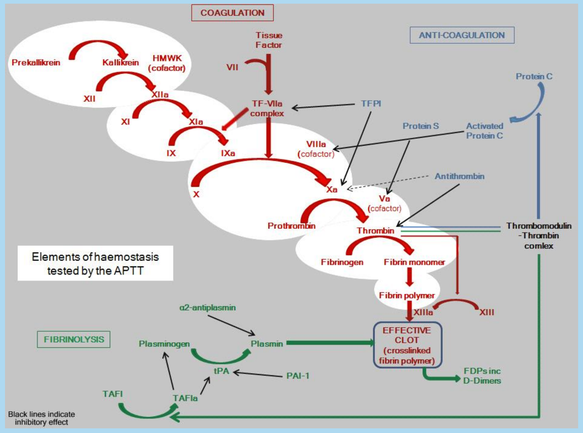

Fig. 2 Coagulation Cascade
http://practical-haemostasis.com/Screening%20Tests/aptt.html

- It is an organic, heterocyclic compound with a phenylpiperidine skeleton containing five hydrogen bond acceptors and one hydrogen bond donor

Fig. 3 Apixaban in the binding pocket

- At physiological pH, apixaban does not ionize, therefore it is neutral allowing for increased absorption, resulting in increased bioavailability.[2]
- Absorption is not affected by food.[2]
- Apixaban has a low volume of distribution (0.31L/kg), which suggests it stays in the main blood compartment where factor Xa is found.[12]
- Apixaban is equally eliminated by the liver, kidneys, and gastrointestinal bile.[10.12]
- CYP34A is the primary metabolizer of apixaban in the liver, resulting in inactive metabolites.[13]
- The three most important optimizations of the Apixaban molecule are:
  - Bicyclic pyrazole group
    - Prevents the carboxamido linker from being hydrolyzed into a mutagenic aniline moiety and increases factor Xa potency
  - C-3 carboxamido moiety
    - Increases potency for factor Xa
    - Binds directly to the active site
    - Exhibited excellent pharmacokinetic parameters.[9]
  - Gamma lactam group
    - The nitrogen in this group greatly increases the potency for factor Xa by forming a lipophilic pi interaction with the Trp215 residue of factor Xa
    - This aligns the entire molecule into the correct position around/in the active site of factor Xa.[9]

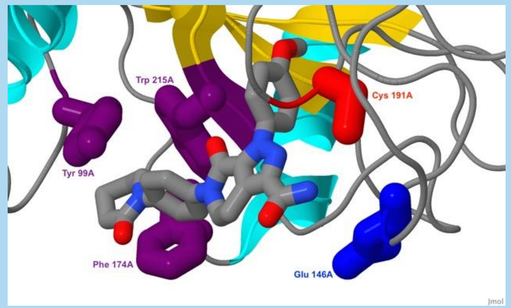

Fig. 4 Apixaban binding interaction with Factor Xa

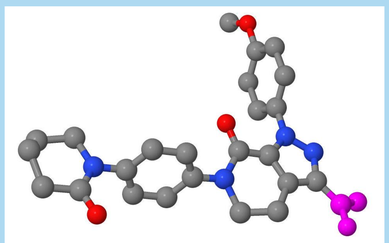

Fig. 6 Apixaban with highlighted C-3 carboxamido moiety

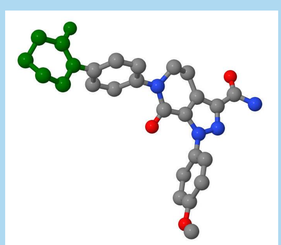

Fig. 7 Apixaban with highlighted gamma lactam group

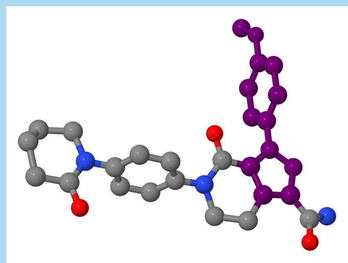

Fig. 5 Apixaban with highlighted bicyclic pyrazole group

The Next Question

- Apixaban works well as a novel anticoagulant
- Major issue with this new drug is lack of an antidote
  - Discovery of a reversal agent is imperative:
    - Overdose
    - Drug-to-drug interactions
    - Emergent surgery situations
  - Bleeding can persist for 24 hours after last dose
  - No conclusive efficacy evidence on known reversal agents
  - Reversal agent is necessary to increase safety due to therapeutic superiority compared to classic anticoagulant drugs such as warfarin
- Apixaban could be more widely used if there was a way to ensure an overdose could be treated

Fig. 8 Apixaban (Eliquis)
http://smp.businesswire.com/sitessmp.newshq.businesswire.com/files/image/imageEliquis_5mg_Box_Bottle.JPG

Summary

Apixaban can be used successfully in patients, despite having a lack of a proven reversal agent. It is a good option for those who cannot tolerate other anticoagulants that are considered first like or are unable or unwilling to commit to the intense monitoring regimen required for warfarin therapy. It is important that patients are counseled on the signs and symptoms of bleeding, regardless if they are on interacting medications or not, and that if bleeding were to occur, to seek medical attention immediately. Apixaban and other novel anticoagulants are becoming more popular as their effectiveness becomes more apparent, due to their straight forward regimen and less intensive monitoring. Therefore, finding a proven reversal agent in the future is becoming more important.

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