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An Update on Oral Anti-coagulants

Deepak Gupta[1]* and Raman Sharma[2]

[1]LECOM Bradenton School of Pharmacy, Bradenton, FL, USA
[2]Department of Pharmacology, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), Pushp Vihar, New Delhi, India

Introduction

Anti-thrombotic drugs generally refer to the group of drugs that prevent either occurrence or enlargement of a thrombus. They can be broadly divided into anti-coagulant (AC) and anti-platelet agents. Alternatively, some anti-thrombotics specifically referred to as thrombolytic, can act by dissolving already existing clots. ACs plays a very significant role in pharmacotherapy and oral ACs is major players in outpatient settings. Main focus of this article will be on oral ACs including application and comparison of newer agents with warfarin, which is still considered a gold standard in AC therapy.

There are total of thirteen AC drugs approved by USFDA (United States Food and Drug Administration) and these drugs act by either diminishing the syntheses of crucial blood clotting factors or directly inhibiting activated factors involved in the coagulation cascade. Although there are thirteen drugs currently in the market, only five of these are available orally. Examples of these drugs are warfarin, dabigatran etexilate, rivaroxaban, apixaban and edoxaban.

Warfarin Compared with Direct Thrombin Inhibitor (DTI)

Warfarin was first approved for human use in 1954 and from the start became a blockbuster drug. One of the earlier patients on warfarin was then US president Dwight D. Eisenhower, following a heart attack [1]. This drug has enjoyed its popularity for the last 60 years and has prolonged millions of lives. Chemically, it is a coumarin derivative and works by inhibiting the formation of vitamin-K dependent clotting factors II, VII, IX and X. While warfarin is a very potent drug; its narrow therapeutic index warrants that this drug needs to be carefully monitored and a fine-tuned therapy is required to minimize side effects [2]. In case of toxicity, like major bleeding, vitamin K is the first line antidote which, if needed, can also be combined with PCC (Prothrombin complex concentrate, KCentra®). For decades, warfarin has continued to be the most used AC in the market. Warfarin has labeled indications for prophylaxis and treatment of thromboembolic disorders (e.g., venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement. It is also used as an adjunct to reduce the risk of systemic embolism after myocardial infarction (MI) e.g., recurrent MI and stroke. Warfarin is the only coumarin currently available in US. Other coumarins like anisindione (originally approved 1957) and phenindione were discontinued due to significant hepatic and renal toxicities.

Another drug in AC drug series that came closest to FDA approval in 2006 was ximelagatran, a direct thrombin inhibitor (DTI). However, extensive hepatotoxicity of this drug led to withdrawal of the application. It took another four years to approve a DTI named dabigatran etexilate mesylate (Pradaxa®) that was regarded as an oral alternative and a stronger competitor of warfarin [3]. Dabigatran etexilate is a prodrug, which when activated *in-vivo,* acts as a specific and reversible inhibitor of thrombin; inhibiting both free and fibrin-bound thrombin. One of the principal advantages of this drug is that routine patient monitoring is not required. Although dose adjustment in special populations (like renal dose adjustment with CrCl ≤ 30) and some compliance concerns have been reported, this drug still offers a very crucial addition to the field of ACs. However, similar to other ACs, bleeding (sometimes fatal) is the most common complication associated with this drug. This concern is further aggravated by the lack of specific antidote for reversing dabigatran's effect. Thus, protamine and vitamin K cannot be useful in case of toxicity due to drug's unique mechanism of action. Boehringer Ingelheim, the manufacturer of dabigatran, is working on bringing specific antidote of dabigatran to the market. Idarucizumab, a monoclonal antibody, has shown promising results in specifically antagonizing the effects of dabigatran. Currently, this drug is in phase 3 clinical trials and has the potential to become the first specific antidote of dabigatran [4]. Approval of this antidote could give momentum to the otherwise stagnant sales of dabigatran. This drug has approved indications for deep vein thrombosis (DVT), pulmonary embolism (PE) and nonvalvular atrial fibrillation (to prevent stroke and systemic embolism).

Factor Xa Inhibitors

Urgent need of newer ACs led to the approval of drugs specifically targeting factor Xa with novel mechanism of action [5-8]. In the last five years, three drugs belonging to this class have been approved. Rivaroxaban (Xarelto®) was the first oral drug in this class that was approved in 2011 [5]. This drug has excellent bioavailability and a good half-life, thus, permitting once a day dosing. Patient compliance, a critical factor in this case, is better for once a day dosing when compared to twice a day dosing regimen of dabigatran. Besides, routine lab monitoring for this drug is not required which is a great advantage when compared to warfarin. However, similar to dabigatran, no specific antidote for rivaroxaban is available in the market and generally; it is recommended to withhold the drug at least 24 hours before the surgery. Besides, the use of non-specific antidotes like activated PCC (aPCC) or recombinant factor VIIa has not been evaluated. Rivaroxaban represents a novel molecule having a unique mechanism of action and despite certain limitations, is proving to be an important drug molecule in the AC therapy. Two additional drugs in this class, apixaban (Eliquis®, 2012) and edoxaban (Savaysa®, 2015), have been recently approved [7]. Following its entry in 2015, edoxaban became the fifth oral drug in the list of ACs [6,8].

With three drugs in the same class, it is important to know characteristics of each drug and which one to use in a particular situation. A detailed analysis of all oral ACs is beyond the scope of this article and thorough information can be found in the published

***Corresponding author:** Deepak Gupta, Associate Professor of Pharmaceutical Sciences, Director-Center for Drug Delivery and Targeting (CDDT), LECOM Bradenton School of Pharmacy, 5000 Lakewood Ranch Blvd, Bradenton, FL 34211, USA, Tel: 941-782-5961; E-mail: dgupta@lecom.edu

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results and clinical trials [9-12]. Briefly speaking, edoxaban is very similar to rivaroxaban and apixaban in terms of mechanism of action, monitoring, reversal strategies and preoperative management. In an indirect comparison analysis of safety and efficacy of edoxaban, it was found that edoxaban was quite similar to apixaban for efficacy endpoints, major bleeding, myocardial infarction and mortality [13]. At this point, all three oral factor Xa inhibitors are FDA approved for DVT, PE and nonvalvular atrial fibrillation (to prevent stroke and systemic embolism). Besides, rivaroxaban and apixaban are also approved for postoperative DVT thromboprophylaxis.

Literature search revealed that there is no head to head comparison analysis of all five oral ACs. Meta-analysis and comparative analysis of clinical trials for warfarin and all three factor Xa inhibitors in atrial fibrillation indicated that major bleeding was lower with apixaban and edoxaban as compared to other two [14].

Discussion

With the arrival for four newer ACs in last five years; warfarin's sixty years monopoly has subsided and one can expect a continuous increase in the use of newer drugs. Each drug has something to offer but also comes with black box warnings, cautions and/or precautions. Newer agents do not require frequent monitoring, has faster onset of action and can directly bind to activated factors both in free as well as clot-bound form. However, these drugs do not have established track record like warfarin and clinical outcome data may not be sufficient for all the situations. Additionally, dosing in special population is always not clear. Another important consideration in the use of these newer drugs is the availability of specific antidotes. So far, no specific antidote is available for any of four new drugs and although aPCC or recombinant factor VIIa may be useful; their clinical impact needs to be carefully evaluated. In case of major bleeding like intracranial hemorrhage, having a specific antidote is very critical. Research in this area is continuously expanding and some initial promising results suggest that specific reversal agents like idarucizumab (monoclonal antibody for dabigatran reversal) [15] or recombinant antidote andexanet alfa (PRT064445) for factor Xa inhibitors [16] may be approved soon. In conclusion, clinicians now have different options to choose from, however, which drug is best suited for a particular patient needs to be evaluated very carefully.

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