Reversal Agents for Oral Anticoagulant Rivaroxaban

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Summary: The oral factor Xa inhibitor rivaroxaban has shown a favorable wellbeing and efficacy profile as compared to the well known anticoagulant drug warfarin for the prevention and treatment of thromboembolic disorders. But treatment with this anticoagulant causes an increased bleeding risk. Bleeding complications can be managed by reversal agents to keep the patient hemodynamically stable until the effect of rivaroxaban weans off. This review highlighted the pharmacological characteristics of various reversal agents including Prothrombin complex concentrate, Activated Prothrombin complex concentrate, Recombinant factor VIIa, Andexan*et al*fa, and Ciraparantag used in the treatment of laboratory parameters prothrombin time (PT) and clotting time (CT) for the reversal of rivaroxaban. Specific antidotes are under development which will assist the clinical administration of severe bleeding events and emergency surgery or life-threatening bleeding. Reversal agents of apixaban have also been highlighted briefly in this manuscript.

Keywords: Rivaroxaban; Anticoagulant; Reversal; Bleeding; Prothrombin; Antidote.

Introduction

Anticoagulation therapy is an important approach to various cardiovascular diseases. Anticoagulation agents prevent new clots and also assist intrinsic mechanisms of clot Convalescence by hindering the accessible clot development.

Rivaroxaban RIV (Fig. 1) an oral anticoagulant, is an orally bioavailable member of a novel class of potent Xa inhibitors that has been prepared by Bayer [1] HealthCare and Ortho-McNeil Pharmaceutical Inc. and sold under the trade name Xarelto®, it was also approved by U.S FDA during the year 2008 [2]. Rivaroxaban is used for the treatment of venous thrombo-embolism in elective orthopedic surgery like total hip and knee replacement, Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), and diminution in the threat of reappearance of PE and of DVT. It is also used for the prevention of stroke in non-valvular Atrial fibrillation (AF) [3-4].

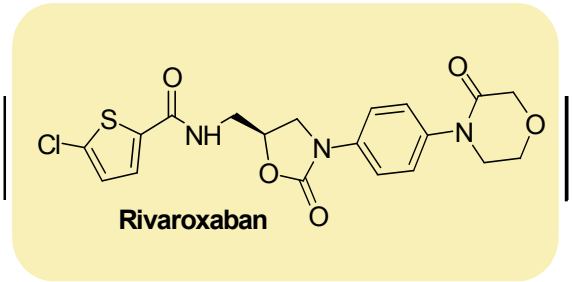

Fig. 1: Chemical structure of rivaroxaban.

RIV not only inhibits the activity of prothrombinase complex but also inhibits free and clot-bound Factor Xa [5], thus suppressing thrombin generation. The half-life of RIV is short as compared to the established oral anticoagulants and is excreted one-third unmetabolised by the kidneys, the remaining two-thirds are equally metabolized to inactive constituents and get excreted by kidneys and liver [6]. Due to the short half-life of RIV, the availability of reversal agent is considered to be unnecessary in many cases [7]. But still there are some circumstances which require laboratory monitoring when the over dosage of the drug causes renal failure, reversal agent may be crucial for emergency reversal of the anticoagulation effect of RIV. Due to these reasons, a great attention has been paid to the development of new reversal agents that quickly reverse the anticoagulation effect of RIV. Number of reviews have been published on the reversal agents of direct oral anticoagulants (DOACs) and novel oral anticoagulants (NOACs) in detail [8-11a] but no individual review has been published so far on the reversal strategies of rivaroxaban separately, in this review we describe the pharmacological characteristics of various reversal agents used for reversing the anticoagulation effect of rivaroxaban drug. Reversal agents of apixaban have also been highlighted briefly in this manuscript.

Clinical aspect of rivaroxaban

Rivaroxaban exhibited conventional pharmacokinetic and pharmacodynamic properties. It

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is swiftly absorbed with maximum plasma concentrations Cmax, happening after 2–4 hours of drug intake with half life 5-9 hours (Fig 1a) [11b]. RIV is metabolized in the liver via hydrolytic and oxidative processes which are catalyzed by cytochrome P450 (CYP) 3A4/5 and 2J2. RIV is also a substrate of efflux transporter protein P-glycoprotein (P-gp) [3a]. The currently approved bioavailability at 10 mg dose is 80-100% [11b]. Rivaroxaban is licensed for preventing stroke and systemic embolism in patients with non-valvular AF having one or more risk factors, such as congestive heart failure; age ≥ 75 years, hypertension and diabetes mellitus. The dose recommended is 20 mg once daily. Rivaroxaban dose for DVT and PE patients is 15 mg twice daily for 3 weeks (20 mg once daily). RIV is not recommended in patients taking azole antimycotics and HIV protease inhibitor, such as Ritonivir. When body weight is between 50-120 kg then no dose adjustment is required. The most common adverse effects that have been produced in RIV treated patients are, pain in extremity, wound secretion, bleeding, muscle spasm and pruitus and blisters [13a].

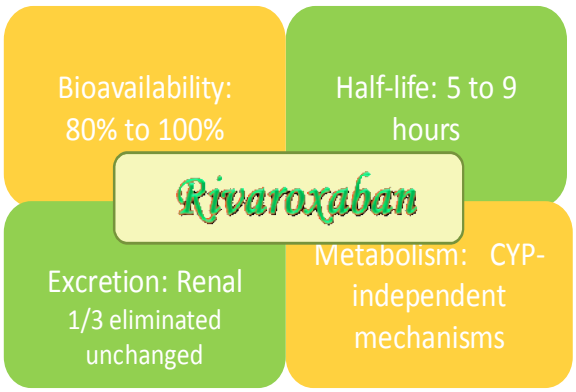


Fig. 1: (a) Pharmacokinetic data of rivaroxaban [3].

Reversal agents for factor fXa inhibitors

Anticoagulants carry a risk of bleeding, in that case, reversal agents commonly known as antidotes may be beneficial in treating severe bleeding. Anticoagulants like RIV with short half-lives are less liable to entail a reversal agent than those anticoagulants with long half-lives because their withdrawal will normalize the hemostasis. Warfarin achieves its peak anticoagulant effect between 72 and 96 hours after the initiation of anticoagulant therapy, in comparison rivaroxaban has 5-9 hours short half-life in younger patients and in the case of elder subjects aged 60-76 years 11-13 hours [12]. Moreover, unlike warfarin, it has an improved bleeding profile in phase III studies [13a]. Apixaban is another oral direct factor (DOACs) Xa inhibitor and has been studied in several clinical trials. Its half-life is 8-15 hours and is 87% protein bound [13b].

The reversal of the anticoagulant effect of RIV may be required in emergency situations, such as in subjects with a life-threatening and serious bleeding event or in the case of urgent surgery. The aPCC, rFVIIa, and PCC are hemostatic agents and contains a high concentration of coagulation factors and due to this property, they may overcome factor Xa inhibition by promoting TG. While rFVIIa and aPCCs are endorsed to stop bleeding in patients suffering from inhibitor-developing hemophilia [14]. Studies in animals and humans have displayed the potential of using these haemostatic agents in reversing RIV-provoked anticoagulation. Several possible approaches Fig. 2 are used to restore physiological hemostasis in patients utilizing an anticoagulant including (1) enhancing the rate of drug clearance (elimination) (2) hemostatic agents (reversal agents) that activate coagulation by alternative pathways (3) replacement of the coagulation factors that are inhibited by the anticoagulant (4) Drug-specific antidotes that neutralize the anticoagulation of the drug [15].

Hemostatic agents for Rivaroxaban

Perzborn *et al*. [16] evaluated the potential of using three hemostatic agents PCC, aPCC, and rFVIIa for the reversal of RIV in human blood. The effects produced by these haemostatic agents in terms of reversal of the RIV anticoagulation effect were compared via several parameters including PT, CT which was measured by TEM, TG (lag time, and ETP. Results showed that all the hemostatic agents were effective in reversing the anticoagulation effect of RIV but the reversal was partial and limited. rFVIIa and aPCC had a higher potential of reversal than PCC. But, reversal was not complete and PT, CT, and TG assays cannot predict the dose of a reversal agent required for reversing the anticoagulation effect.

Various studies demonstrated improvements in coagulation assays and TG with the treatment of either of the hemostatic agents PCC, aPCC, and rFVIIa (Table-1).

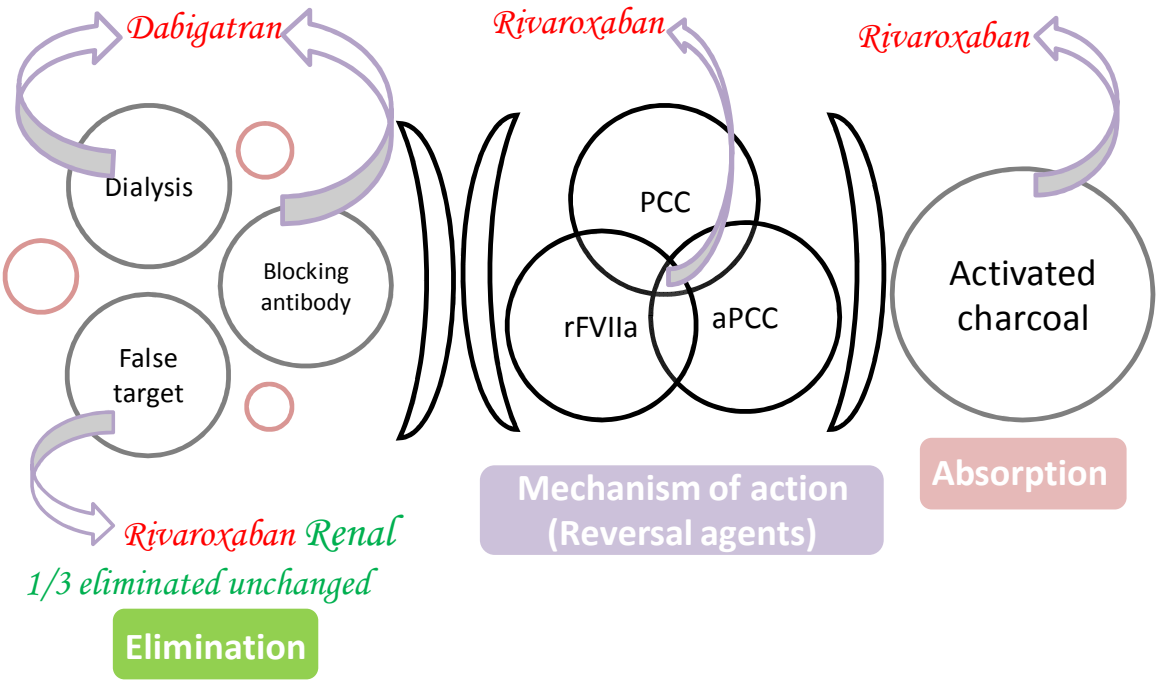


Fig. 2: Reversal strategies for the oral anticoagulants fXa inhibitors to restore physiological hemostasis [15].

Table-1: Improvements in TG and coagulation assays in-vitro and in human volunteers with addition of PCC, aPCC, and rFVIIa (Rivaroxaban)

Agents	Ex-Vivo Model	Animal Model	Human Volunteers
PCC	Illustrated some improvement in PT, CT, and TG but not as much effective as aPCC or rFVIIa. [16] Various studies demonstrated no change or only some improvement in TG	Reduced PT and bleeding time in baboons and rats. [18]	Improvement of laboratory parameters including PT, TG four factor concentrate reduces the PT>3 factor but improves TG more [19]
aPCC	Demonstrated the most efficient reversal of PT, CT, and thrombin potential as compared with aPCC and rFVIIa. [16]	Reduced PT and bleeding time in baboons and rats. [18]	Improvement in laboratory parameters which includes PT and thrombin potential [20]
rFVIIa	some correction of TG and CT. [17]	Reduced PT and bleeding time in baboons and rats. [18]	Improvement in laboratory parameters which includes PT and thrombin potential [20]

Prothrombin complex concentrate (PCC)

PCCs are derived from plasma and contain changeable amounts of vitamin-K-dependent coagulation factors such as II, IX, and factor X (3-PCC contain 3-factors known as 3-factor PCC) or factors II, VII, IX, and X (PCC carrying 4 factors known as 4-PCC) containing varying amounts of the proteins S and C. PCCs having factor VII are called as 4-factor PCC while PCCs which lack factor VII are called as 3-factor PCC. Clinical Data related to the effectiveness of PCC for reversing the anticoagulation effect of anticoagulants in patients with severe bleeding problems are lacking. Healthy subjects taking 20 mg RIV twice daily for 2.5 days, an excerpt of 4-PCC with an amount of 50 U/Kg corrected the prolonged PT and abnormalities in ETP. Wherein the 4-PCC did not correct the extended CT and aPTT. The administration of 4-factor 4-PCC to RIV-treated rabbits partially corrected the laboratory parameters but is unable to reverse the bleeding, and no normalization of TG lag time and PT was noted but only partial normalization of AUC (area under the curve) was observed [21]. In the use of PCC, there is a risk of thrombotic complications happening at 1.4% rate when utilized to indulgence VKA-associated bleeding [22]. PCC among other reversal agents has been recommended as an antidote for reversing the anticoagulation effect of RIV [23]. Eerenberg *et al.* [20] demonstrated the full reversal of RIV in healthy volunteers upon PCC administration as measured by TG and PT. While ex-vivo study carried out by Marlu *et al*. [24] demonstrated only incomplete normalization of TG lag time and

overcorrection of TG upon in-vitro PCC spiking of plasma obtained from healthy volunteers on RIV anticoagulation therapy. These results indicate differences in the retort with regard to human and animal ex-vivo and in-vitro models.

Dinkelaar *et al*. [18] demonstrated the suitability of the PT innovin assay and a diversity of TG assays such as ETP plasma assay (Siemens) and CAT, thrombinoscope employing various TF concentrations [25, 26] as well as the entire blood TG assay [27] in monitoring the RIV anticoagulation reversal by PCC. Results showed that PCC does not neutralize the enhancement on Lag time and PT of the RIV anticoagulated blood in-vitro. Nevertheless, potential of total TG can be standardized. The quantity of PCC needed for this normalization depends on both the TF concentrations and the presence of a cellular component.

Levi *et al*. [28] evaluated 3-PCC for the reversal of RIV in an open-label, single-center, and parallel-group, in-vivo study of 35 healthy subjects. The adults were given 20 mg of RIV twice daily for 4 days followed by a single 50-unit/kg dose of either 3-PCC or 4-PCC or a control. The 3-PCC produced a smaller reduction in PT as compared to 4-PCC, but 3-PCC more effectively reversed endogenous thrombin ETP.

Activated PCC (aPCC)

aPCC holds plasma which contains activated coagulation factors such as II, VII, IX, and factor X. aPCC was introduced as a prohemostatic agent for the cure of hemophilia in subjects with inhibitors to factors VIII and IX [29]. aPCC is commercially available as factor VIII inhibitor bypassing activity or FEIBA. In animals, aPCC has been revealed to reverse the anticoagulation of high-dose RIV [30]. Data obtained from *in-vitro* assays indicates that aPCC corrected the anomalous TG parameters when mixed with the blood of patients receiving a high dose of RIV (20 mg) [31]. Pharmacovigilance data illustrated the low threat of thrombosis (4–8 events per 105 infusions) in hemophilia patients receiving aPCC. While the majority of the events almost 81% occurred in subjects with thrombotic threat factors [32].These data elevates concerns regarding aPCC use in subjects getting anticoagulant treatment for the treatment and preclusion of thrombotic diseases. Another animal study in baboons infusion of aPCC corrected the prolonged PT occurred due to high doses of rivaroxaban [33]. Animal models have demonstrated the effect of 4-PCC on RIV in murine ICH (intracerebral hemorrhage) models [34]. Murine models in mice exposed to incrementally large doses of RIV with induction of ICH found that administration of 4-PCC prevented expansion of hematoma more consistently than did rFVIIa in RIV associated bleeding [34]. The use of 4-PCC and aPCC was described by Escolar and colleagues [31] in an in-vitro model using the blood of 10 healthy human subjects. The 4-PCC was the least effective to correct CT prolongation as compared to the other factor concentrations. 4-PCC and aPCC were more effective than the rFVIIa in improving TG.

Recombinant factor VIIa (rFVIIa)

rFVIIa, a prohemostatic agent was build up mainly as a bypassing agent in hemophilia patients with antibodies to FVIII but the off-label use of rFVIIa has swiftly enhanced. rFVIIa had no effect on aPTT or irregular TG. rFVIIa also failed to improve bleeding problems in rabbits receiving the RIV. Use of rFVIIa is associated with an increased rate of thromboembolic events as compared with those receiving placebo {5.5% vs 3.2%; 95% confidence interval 1.20-2.36 and relative risk 1.68} [28]. This agent had no effect on bleeding but reduced the bleeding time in rabbits receiving rivaroxaban via Folts injury model [21]. Baboons treated with supratherapeutic doses of rivaroxaban showed some reduction in bleeding time but no normalization of the PT and the bleeding time when given high doses of rFVIIa (210 mg/kg).

Körber *et al*. [35] evaluated the effect of rFVIIa to reverse prophylactic and therapeutic RIV levels in-vitro and to monitor rivaroxaban with thromboelastometry and reversal therapy with aPCC. RIV prolongs the CTExTem significantly in prophylactic and therapeutic concentrations. Reversal with aPCC and rFVIIa causes a decrease of CTExTem, thus aPCC and rFVIIa was found to be potent antidotes for RIV. aPCC and rFVIIa decrease CT and PT in the 50 IU/kg BW aPCC significantly.

Andexanet alfa (PRT064445)

PRT064445 is a universal reversal agent being developed by Portola Pharmaceuticals, is able to dose-dependently reverse the anticoagulation effect of RIV *in-vitro* [36]. It is a novel recombinant modified protein that is parallel to local factor Xa. It binds to factor Xa inhibitors in the blood thus avoiding them from inhibiting the action of the native factor Xa. PRT064445 is effectively a decoy compound having a high-attraction binding for factor FXa inhibitors and causes a fast diminution of the free plasma concentration and neutralization of the

anticoagulation effect of the RIV. This discharges the inhibition of factor FXa in the prothrombinase complex, which consequences in the formation of thrombin [37] (Fig. 3). PRT064445 also corrected the PT prolongation produced by RIV. In the similar study, PRT064445 when administered to rats in-vivo receiving RIV infusions quickly lessened the INR. In rats treated with RIV, PRT064445 reduced the plasma concentrations of free RIV, the portion which is responsible for mediating the anticoagulation. Abnormalities in aPTT, PT, and anti-Xa assays were corrected, loss of blood minimized when PRT064445 was administered to rabbits taking the RIV in a liver laceration model [37].

Hollenbach *et al*. [38] used rabbit liver laceration model to evaluate the effects of andexan*et alf*a to invalidate the RIV effect. rFVIIa was also tested in the similar model for the sake of comparison. Anesthetized rabbits were injected vehicle or 1 mg/kg of RIV followed by the andexan*et alf*a and rFVIIa and followed by a slash of two liver lobes. RIV resulted in 2.3-fold and 1.9-fold prolongation of aPTT and PT parameters and enhanced blood loss. Andexan*et alf*a reduced this blood loss by >85% with reduced peak anti-fXa activity by 98%, PT by 74% and aPTT by 66% while the free fraction of RIV in plasma from 26% to <0.5%, rFVIIa has no effect on blood loss.

In human volunteers, RIV [39] was injected at an oral dose of 20 mg for 6 days and then andexan*et alf*a was directed intravenously after 3 hours. Immediately after achievement of the 210 mg and 420 mg doses, anti-FXa activity reduced in a dose-dependent manner by 20% to 53%. The plasma concentration of unbound RIV was reduced by 32% and 51% relative to pre-andexanet values. RIV-induced inhibition of TG and prolongation of both ACT and PT were also quickly reversed by andexan*et alf*a dose-dependently. There was no increase in prothrombin portions F1+2, D-dimer or thrombin-antithrombin. There were also no thrombotic events or harsh unfavorable effects. In human volunteers 50-75 years old, an intravenous andexanet bolus of 400 or 800 mg transiently and quickly reversed over 90% of the anti-FXa activity of RIV.

The PER977 (ciraparantag) (Fig. 4) is a small, synthetic, cationic and water-soluble molecule developed by Persosphere Inc and is under analysis as a potential antidote for RIV [40]. PER977 binds non-covalently to rivaroxaban thereby inhibiting its anticoagulant effect. PER977 reduced bleeding in a standard rat tail model and also in ex-*vivo* human plasma when treated with RIV. With the use of PER977, no significant adverse effects have been observed in animal models. In a rat model, ciraparantag reduced bleeding by > 90 % when administrated in a condition where the rats receive 100 times overdose of RIV. In a rabbit liver laceration subject, blood loss was decreased to a related degree when 30 mg/kg of PER977 were given. Clinical trials are expected to start soon to further explore the reversal effect of PER977.

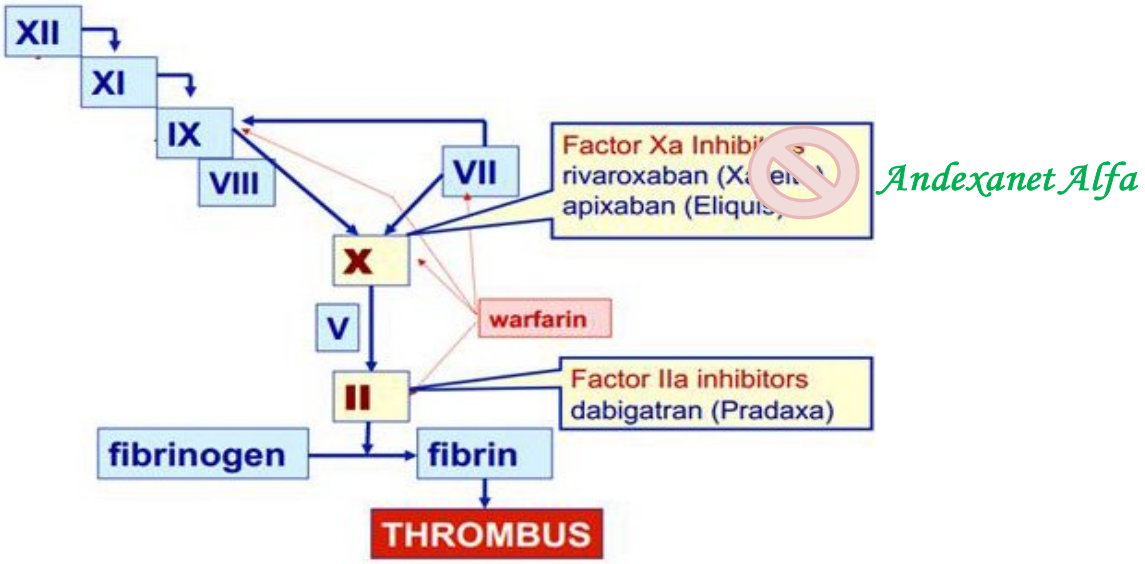
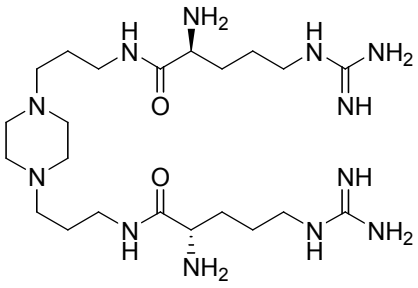


Fig.3: Andexan*et alf*a on coagulation cascade [37].

PER977 (ciraparantag)



Ciraparantag

Fig. 4: Chemical structure of ciraparantag.

Activated oral charcoal (AC)

Rivaroxaban does not bind to activated charcoal and due to its rapid absorption, gastric lavage is unlikely to be useful unless utilized almost instantly after ingestion. However AC is most commonly used in the management of drug poisoning and overdoses and can modify the pharmacokinetics of many drugs.

Ollier *et al*. [41] quantify the impact of AC on RIV in healthy adults in an open-label study with an incomplete cross-over design of single 40 mg RIV dose administered either alone or with AC in 12 healthy subjects. AC significantly reduces RIV exposure at 2, 5 and 8 h post-dose. Even Ac administration up to 8 h post-dose decreases the RIV exposure, this suggests that AC could be used in RIV overdose poisoning and accidental ingestion to alienate absorption.

Hemodialysis

Due to the significantly high protein binding (95%) [42] of RIV, hemodialysis is unlikely to remove this drug and RIV may not be dialyzable. Charcoal hemoperfusion eliminates the highly protein-bound drugs, but is not accessible in routine and has not been practiced to eliminate RIV.

Apixaban

To the best of our knowledge, there is no specific antidode available for apixaban for carrying out the clinical studies. Some clinical reports can be found for the reversal of apixaban using Prothrombin complex concentrate (PCC) and Recombinant factor VII. Portola compound is in phase II appraisal.

The animal model in-vivo study demonstrated the effect of PCC, rFVII, and Clottafact (fibrinogen) in rabbits receiving apixaban [43]. Rabbits were administered apixaban with dose 0.4 mg/kg bolus, with 0.6 mg/kg/hr infusion, after randomization they receive PCC 60 IU/kg, rFVII 240 mcg/kg and fibrinogen 300 mg/kg. Apixaban considerably enlarged hepatosplenic blood loss and bleeding times as compared to control. Administration of these reversal agents did not reduce hepatosplenic blood loss, nevertheless, both rFVII and PCC partially reverse bleeding time to 83.5 sec. whereas fibrinogen increase both bleeding time and blood loss in apixaban treated rabbits. Though fibrinogen enhanced endogenous thrombin potential (ETP). Apixaban increased PT, but no effect was observed on aPTT. Only rFVII regularized prolonged PT values, PCC was unable to normalize prolonged PTs [43]. There are fewer data found on the use of PCC and aPCC in case of apixaban as compared to rivaroxaban. There is currently no specific reversal agent available for apixaban. However, andexan*et al*fa has been tested in an animal model, but is currently undergoing clinical examination and is not available for the clinical trial [44].

Apixaban is highly protein bound like rivaroxaban there is no role for hemodialysis in the management of bleeding associated with apixaban use [45]. Charcoal administration after 2-6 hours infusion of 20 mg apixaban to healthy volunteers decreased the area under the curve but no effect was observed on the Cmax [46]. Charcoal reduced the half-life of apixaban. Despite the limited literature available the same reversal agents and strategies used for rivaroxaban as described above may be applied for apixaban because of their similar mechanism of action. Table-2 summarizes the reversal agents of apixaban. No human studies have been found in the literature as in case of rivaroxaban. Only some reports have been found on animal models but PCC and aPCC has no effect on blood loss.

Table-2: Improvements in TG and coagulation assays by addition of PCC, aPCC, and rFVIIa (Apixaban)

Agents	Ex-Vivo Model	Animal Model	Human Volunteers
PCC	Improved thrombin generation (TG) [31]	Some improvement in laboratory parameters but has no effect on blood loss [43]	No evidence
aPCC	Improved the CT, TG, and the clot formation time [31]	No evidence	No evidence
rFVIIa	Improved the CT, TG, clot formation time and thedeposition of platelet [31]	Reduced bleeding time in rabbits but has no effect on blood loss [43]	No evidence

Perioperative management

The administration of subjects under the effect of anticoagulant agents is one of the common challenge in thoracic surgery. Many patients on anticoagulant therapy require temporary disruption of the therapy in the perioperative period, in this case, a careful balance between bleeding and thromboembolic events is required. Direct oral anticoagulants (DOACs) usually possess comparatively shorter half-lives as compared to warfarin. Warfarin has a long half-life at 72-96 hours and because of this long half-life, the 2012 CHEST guidelines advised the discontinuation of warfarin 5 days former to surgery and then restarted 12 to 24 hours after the surgery when sufficient hemostasis has been recognized [47]. RIV has a half-life of 5-9 hours and is recommended to be discontinued no less than 24 hours prior to a method and then restarted as soon as enough post-operative hemostasis is created [3, 48]. The half-life of apixaban is 12 hours, its discontinuation before surgery is dependent on the risk of surgically persuade bleeding. If the bleeding risk is high then apixaban should be discontinued 48 hours former to surgery and if the surgical bleeding risk is low then it should be discontinued 24 hours prior to surgery and then restarted after the hemostasis is established [49]. To avoid the risk of high bleeding RIV should be prescribed with great caution or shunned in subjects using anti-platelet therapy. Bleeding sometimes can be fatal and enhanced the danger of death. For that reason, the administration of anticoagulants should be evaluated and checked carefully.

Discussion

The oral anticoagulants cause life-threatening bleeding and patients may necessitate emergency surgery. Education regarding the use of anticoagulants is necessary to guarantee patients and the healthcare professionals do not continue to administer the anticoagulants in the event of serious bleeding or symptoms that may need emergency surgery. In case of potentially life-threatening bleeding, additional management may be deemed, such as PCC, aPCC, and rFVIIa. Though none of these reversal agents have been illustrated to be effective in clinical methods involving hemorrhage patients, only animal studies, volunteer studies and in vitro experiments showed the evidence. There is no consensus, on which of these reversal agents is superior and their dose. PCC is cheaper and because of its indication for warfarin anticoagulant, reversal is more quickly available as compared to aPCC or rFVIIa. aPCC encompass activated clotting factors and would be more efficient in ending bleeding as compared to PCC reversal agent, but it is more thrombogenic and may increase the risk of superfluous thrombosis. Thromboembolism is one of the potential complications of PCC use happening at a rate of 1.4% when used for the treatment of Vitamin K antagonists (VKA) associated bleeding [22]. These reversal agents may offer the most effectual process of reversal. PER977 have the advantage of reversing all the oral anticoagulants along with heparin but its mechanism is still unclear. rFVIIa is used for bleeding complications in hemophilia patients, but its use outside its indication cause increased the risk of arterial thromboembolism. PRT064445 reduced anti-xa activity and plasma concentrations of free apixaban.

Conclusions

In conclusion, the current review focused the several reversal agents PCC, aPCC, rFVIIa, PRT064445, and PER977 used for the reversal of rivaroxaban and apixaban in the case of severe and life-threatening bleeding episodes. But the studies demonstrated partial reversal of rivaroxaban and much research is required to identify the most reliable reversal agents and develop and implement safer, efficient and reliable assays to steer reversal of the rivaroxaban. Further clinical guidelines for laboratory testing of rivaroxaban anticoagulation reversal by antidotes are therefore of greatest importance. Antidotes (idarucizumab, ciraparantag, and andexan*et al*pha) are still under development which will assist life-threatening bleeding. All these reversal agents proffer a great step in the extensive utilization of anticoagulants (rivaroxaban and apixaban) for more customized management.

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