Reversal of Target-Specific Oral Anticoagulants

4

Walter Jeske

Introduction

Anticoagulation is used to prevent thromboembolism following orthopedic surgery, in patients with atrial fibrillation and to treat acute venous thromboembolism. Short-term anticoagulation has traditionally been provided by the administration of heparin (or low molecular weight heparin), while long-term anticoagulation has been achieved through the administration of a vitamin K antagonist such as warfarin. Both heparin and warfarin produce their anticoagulant effects through the inhibition of multiple coagulation factors. Heparin, by binding to antithrombin, inhibits thrombin, factor Xa, factor IXa and, to a lesser extent, other intrinsic pathway factors while warfarin, by antagonizing vitamin K, prevents the formation of active forms of coagulation factors II, VII, IX, and X.

In recent years, several target-specific oral anticoagulants (TSOAC) have been introduced to clinical practice as alternatives to the use of warfarin. These drugs include the factor Xa inhibitors apixaban (Eliquis, Bristol-Myers Squibb, Princeton, NJ-Pfizer, New York, NY), rivaroxaban (Xarelto, Bayer Healthcare, Leverkusen, Germany), and edoxaban (Savaysa, Daiichi Sankyo, Tokyo, Japan) and the thrombin inhibitor dabigatran etexilate mesylate (Pradaxa, Boehringer-Ingelheim, Ridgefield, CT). Another factor Xa inhibitor, betrixaban (Portola, South San Francisco, CA), is in development. These target-specific oral anticoagulants offer advantages over warfarin in that their onset of action is much faster, typically ranging from 1 to 4 h post-dose, the half-life of drug action is shorter, ranging from 5 to 9 h for rivaroxaban to approximately 13 h for dabigatran and no food or drug interactions have been reported. These properties translate clinically into more reliable plasma drug concentrations that do not need to be routinely monitored. These agents have shown favorable efficacy profiles in comparison to standard warfarin therapy in a variety of clinical conditions including the prevention of stroke in patients with non-valvular atrial fibrillation.

The major side-effect associated with the use of anticoagulation is an increase in the occurrence or intensity of bleeding that can range from nuisance value to life threatening. Such enhanced bleeding can occur in response to injury or trauma; or when anticoagulation is supratherapeutic bleeding can occur spontaneously. Although clinical trials have shown that the safety of these new drugs in terms of the incidence of major hemorrhage is similar or better than that observed with conventional therapies, major hemorrhage can still occur.

W. Jeske, Ph.D. (✉)
Cardiovascular Institute, Loyola University Chicago
Health Sciences Division,
2160 S First Ave, Maywood, IL 60153, USA
e-mail: wjeske@luc.edu

© Springer International Publishing Switzerland 2016
C.M. Loftus (ed.), *Anticoagulation and Hemostasis in Neurosurgery*,
DOI 10.1007/978-3-319-27327-3_4

Increased levels of anticoagulation with warfarin, as measured by an International Normalized Ratio (INR) greater than 4.0, are associated with an increased risk of developing an intracerebral hemorrhage (ICH) [1] and warfarinized patients have an increased risk of hematoma expansion compared to patients with ICH who are not anticoagulated [2]. It is estimated that approximately 50 % of warfarin-treated ICH patients will experience hematoma expansion and of these, nearly half will experience a fatal outcome.

Each of the target-specific oral anticoagulants has been tested versus warfarin for their ability to prevent stroke and/or systemic embolism in patients with atrial fibrillation. In each study, the tested dose of TSOAC was associated with a lower rate of ICH compared to warfarin. In the RE-LY study, intracranial hemorrhage was observed in 0.32 %/year of patients treated with dabigatran compared to 0.76 %/year in warfarin-treated patients [3]. In the ROCKET-AF study, the rates of ICH were 0.8 and 1.2 %/year, respectively, for rivaroxaban and warfarin-treated patients [4]. In the ARISTOTLE study, the rates of ICH were 0.33 and 0.8 %/year, respectively, for apixaban and warfarin-treated patients [5]. In the ENGAGE-AF study, the rates of ICH were 0.39 and 0.85 %/year, respectively, for edoxaban and warfarin-treated patients [6].

To minimize the chances of hematoma expansion, it is necessary to reverse the anticoagulation. Lowering the INR to ≤1.3 within 2 h has been shown to have beneficial preventative effects on hematoma expansion. While anticoagulation due to warfarin can be reversed by the administration of vitamin K, this effect takes some time as new coagulation factors are being synthesized. In cases where emergent reversal is necessary, the administration of prothrombin complex concentrates to replace active coagulation factors can be used.

Agent-specific or mechanism-specific reversal agents are not currently available for the target-specific oral anticoagulants leading to concern about what can be done in cases of overdose or in medical emergencies. A variety of approaches to reverse anticoagulant activity or hemorrhage have been tested using in vitro systems, ex vivo using blood samples from anticoagulated subjects, and in vivo using animal models and healthy individuals.

Activated Charcoal

In cases of purposeful or accidental overdose, or when an adverse event occurs shortly after TSOAC administration, it may be desirable to prevent the anticoagulant from reaching the circulation. In an in vitro study, addition of **activated charcoal** to solutions of dabigatran resulted in a reduction in the concentration of free dabigatran in solution [7], suggesting that administration of activated charcoal may be effective in preventing dabigatran absorption in the case of overdose. Although reports of its effectiveness in patients are not available, the administration of activated charcoal has been recommended for treatment of TSOAC overdose, if the anticoagulant was administered within the previous 2–3 h.

Hemodialysis

Dialysis can be used to remove excess concentrations of some drugs from the circulation. While this would be ineffective for reducing circulating plasma concentrations of rivaroxaban and apixaban, owing to their high levels of protein binding (95 and 87 %, respectively), there is some evidence to suggest its benefit for removing dabigatran, which exhibits a much lower level of protein binding. In patients with ESRD given a single 50 mg dose of dabigatran, hemodialysis was shown to reduce plasma dabigatran concentrations by 60–70 % after 2–4 h of dialysis [8]. Similar reductions was observed following high-flux intermittent dialysis in a series of patients receiving the standard twice daily 150 mg dose of dabigatran who were admitted to hospital due to life-threatening bleeding [9]. Mean clearance of dabigatran by veno-venous hemodiafiltration in a patient presenting with

dabigatran overdose was estimated to be 32–58 ml/h [10]. A concern with using dialysis to remove dabigatran is the potential for dabigatran levels to rebound after completion of dialysis as drug redistributes to the plasma compartment. This has led to a recommendation to use prolonged intermittent dialysis or intermittent dialysis followed by continuous renal replacement therapy.

Nonspecific Reversal Agents

Since the TSOACs do not yet have specific reversal agents, reversal of their activity has focused on the off-label use of prothrombin complex concentrates (**PCC**) as factor replacement therapy and the use of pro-hemostatic agents such as rFVIIa in a variety of experimental paradigms. PCCs are a family of human plasma-derived products that have been used to treat hemophilia and more recently for warfarin reversal. PCCs contain varying amounts of coagulation factors and are divided into the categories of three factor products (containing factors II, IX and X), four factor products (containing factors II, VII, IX, and X) and activated PCC (containing factors II, VIIa, IX and X). In addition to having varying relative levels of these factors, some products may also contain anticoagulant substances such as Protein C, Protein S, Protein Z, antithrombin, or added heparin. **Recombinant FVIIa** (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is used clinically to treat and prevent bleeding in hemophilic patients and has also been tested as a potential reversing agent for target-specific oral anticoagulants.

Evidence to demonstrate that nonspecific reversal agents can reverse anticoagulation produced by TSOACs exists on several levels. In the simplest system, addition of activated PCC to dabigatran- and rivaroxaban-supplemented plasmas has been shown to reverse the inhibition of thrombin generation. Supplementation of activated PCC was also shown to be more effective than PCC or rFVIIa at reversing apixaban-induced alterations in thrombin generation and fibrin clot structure [11].

Animal Studies

Animal models that are utilized to assess the relative hemorrhagic potential of anticoagulant drugs involve making a standardized wound in treated animals and measuring the bleeding time or quantitating the amount of blood lost. Such models have been applied to the question of how to reverse TSOAC-induced bleeding. In a mouse tail transection model, aPCC or a combination of PCC + rFVIIa shortened the dabigatran-induced prolongation of bleeding time, but did not reduce the total amount of blood lost [12]. Similarly, in rats, dabigatran etexilate resulted in a prolongation of bleeding time that was reversed by the subsequent administration of three factor PCCs, four factor PCCs, activated PCC and rFVIIa [13, 14]. FVIIa effectively reduced rivaroxaban-induced bleeding time but not blood loss in a rabbit model [15]. Four-factor PCC has been shown to be effective in reducing bleeding following liver laceration in dabigatran-treated animals and following kidney laceration in rivaroxaban-treated animals [16]. Animal studies have also pointed out that stoppage of bleeding following administration of PCC or rFVIIa did not necessarily correlate with a complete reversal of plasma clotting time prolongation.

Intracerebral hemorrhage has been modeled in mice by intrastriatal injection of collagenase. In this model, anticoagulation with either rivaroxaban or dabigatran increased the hematoma volume compared to that seen in non-anticoagulated mice [17, 18]. In rivaroxaban-treated mice, PCC, rFVIIa, and fresh frozen plasma administered 30 min after collagenase treatment prevented excess intracerebral hematoma formation. In dabigatran-treated animals, PCC was more effective than fresh frozen plasma and rFVIIa was observed to be ineffective at preventing hematoma expansion.

Humans: Healthy Volunteers

Several studies using healthy human volunteers have been carried out which demonstrate the ability of PCCs or rFVIIa to reverse anticoagulant

effects of dabigatran and rivaroxaban. In one study, blood samples were drawn from volunteers 2 h after they had received a single dose of either rivaroxaban or dabigatran [19]. Rivaroxaban was observed to prolong the time until initiation of thrombin generation and reduce the total amount of thrombin formed while dabigatran only prolonged the time until thrombin generation began. Supplementation of activated PCC or rFVIIa to the plasma samples normalized the lag time to thrombin generation initiation. Supplementation of either four-factor or activated PCC normalized the amount of thrombin generated.

In a randomized double-blind placebo controlled study in 12 healthy volunteers, repeated dosing of rivaroxaban or dabigatran prolonged clotting time and inhibited thrombin generation [20]. Following the fifth dose of anticoagulant, a single bolus dose (50 IU/kg) of a four-factor PCC was infused over 15 min. Serial blood samples were collected to measure a variety of coagulation parameters. Rivaroxaban significantly prolonged the prothrombin time and inhibited thrombin generation. Both effects were rapidly reversed upon administration of PCC. The anticoagulant effect of dabigatran was observed as prolongations of the aPTT, thrombin time and ecarin clotting time. Administration of four-factor PCC did not reverse any of the prolongations of clotting time. Administration of a lower dose of PCC (37.4 IU/kg) was subsequently shown to significantly increase thrombin generation in healthy volunteers treated with rivaroxaban [21].

One study has been carried out in healthy volunteers using bleeding as an endpoint [22]. In this randomized, double-blind, placebo controlled phase I study, volunteers were anticoagulated with a single oral dose of the factor Xa inhibitor edoxaban followed 2 h later by an infusion of one of three doses of four-factor PCC. Thirty minutes after completion of PCC infusion, a punch biopsy was performed. Four-factor PCC dose-dependently reversed the effects of edoxaban on bleeding duration, bleeding volume, thrombin generation and prothrombin time with a complete reversal of the prolongation of bleeding duration, the increase in bleeding volume, and the inhibition of thrombin generation observed at the highest dose of PCC tested (50 IU/kg).

Humans: Case Reports

Currently lacking in the literature are clinical studies to demonstrate the effectiveness of PCCs or rFVIIa to reverse hemorrhagic effects in patients treated with TSOACs. A variety of case studies, however, have been reported, which demonstrate variable effectiveness of the reversal therapies. The usefulness of aPCC (administered at doses ranging from 42 to 100 IU/kg) or PCC (2000 IU) to treat patients with potentially life-threatening bleeding brought about by dabigatran administration has been suggested [23, 24].

Guidelines

With a lack of clinical trial data to guide the usage of nonspecific reversal agents, a number of authors and professional societies have developed algorithms for dealing with bleeding brought on by the use of TSOACs [25–28]. Each of these strategies incorporates risk stratification to target the appropriate intervention. For minor to moderate bleeding, these guidelines suggest stopping anticoagulation if the perceived benefit of stopping outweighs the risk of continuing and using local compression and transfusion of blood components as necessary. Treatment with nonspecific prohemostatic agents (PCCs and rFVIIa) or removal of the drug by the administration of activated charcoal or the use of hemodialysis should be reserved for those patients with severe or life-threatening bleeding.

Future Agents

Efforts are being made to develop agents that will prevent TSOACs from expressing anticoagulant activity rather than trying to overcome the anticoagulation as is done with the PCCs and rFVIIa. Several more specific antagonists are currently under development. One of these is a modified form of factor Xa (PRT064445; **Andexanet alfa**; Portola Pharmaceuticals) which is catalytically inactive due to a mutation of the serine residue at the active site and also lacks a membrane-binding γ-carboxyglutamic acid domain [29]. This factor Xa variant retains its ability to bind to factor Xa inhibitors and acts as a decoy by binding direct Factor Xa inhibitors or heparin-activated antithrombin and allowing native factor Xa to express its hemostatic function.

Andexanet alfa

In in vitro assays, supplementation of andexanet alfa was shown to inhibit anti-factor Xa activity induced by a variety of direct factor Xa inhibitors. Administration of andexanet alfa to animals anticoagulated with direct factor Xa inhibitors (betrixaban, rivaroxaban, apixaban) or antithrombin-dependent factor Xa inhibitors (enoxaparin, fondaparinux) was shown to reverse the anticoagulant effects measured ex vivo, and to reduce blood loss caused by standardized wounds.

Phase III, randomized, double-blind, placebo controlled trials are being conducted to assess the ability of andexanet alfa to reverse anticoagulation with rivaroxaban (ANNEXA-R study) or apixaban (ANNEXA-A study). The primary outcome for these studies is the reversal of anticoagulation as assessed by the percent change in anti-Factor Xa activity from baseline to nadir, with secondary endpoints being plasma levels of unbound rivaroxaban or apixaban and the change in thrombin generation. Both studies have shown the effectiveness of a single bolus of andexanet alfa to rapidly and significantly reverse anticoagulant activity. An additional arm in each study to evaluate bolus plus infusion dosing of andexanet alfa are ongoing. A phase 4 open-label study in patients anticoagulated with apixaban, rivaroxaban or enoxaparin who present with an acute major bleed is being initiated.

Idarucizumab

Idarucizumab (BI655075, Boehringer Ingelheim) is a humanized antibody fragment that is being developed as an antidote for dabigatran. This antibody fragment has been shown to reverse dabigatran-induced anticoagulant activity when added in vitro to dabigatran-supplemented plasma and when infused to dabigatran anticoagulated rats [30]. Correlating with this decrease in anticoagulant activity was a decrease in rat tail bleeding time. Similarly in a porcine model of blunt hepatic trauma, anti-dabigatran Fab was shown to reverse dabigatran anticoagulation [31].

A number of human studies using idarucizumab to reverse dabigatran have been carried out or are ongoing. A phase 1 study has indicated that onset of action of idarucizumab can be detected immediately following a 5 min infusion. Administration of idarucizumab to dabigatran-treated healthy volunteers restores wound site fibrin formation. Safety, tolerability and PK/PD of idarucizumab has been investigated in a randomized double-blind, placebo-controlled cross over study in healthy subjects and patients with mild/moderate renal impairment who were treated with dabigatran (220 mg bid or 150 mg bid, respectively) for 4 days to achieve steady-state anticoagulation. Complete reversal of anticoagulation was observed at the end of the infusion period. The RE-VERSE AD trial (NCT 02104947), a Phase 3 case series clinical study, will determine the effectiveness of idarucizumab to reverse anticoagulation in dabigatran-treated patients who present with uncontrolled bleeding or who require emergency surgery or procedures. The primary endpoint is the maximum reversal of anticoagulant effect measured by dilute

thrombin time or ecarin clotting time within 4 h of infusion. Secondary endpoints include reversal of other anticoagulant parameters, the occurrence of intraoperative or 24 h postoperative major bleeding in patients undergoing surgery and the time to cessation of bleeding in patients presenting with overt hemorrhage. The study is expected to be completed in early 2017.[1]

Per977

Per977 (aripazine, Perosphere, Danbury, CT) is a synthetic, positively charged, small molecule that has been shown to bind with heparins and a wide variety of direct oral anticoagulants including rivaroxaban, apixaban, dabigatran and edoxaban via hydrogen bonding or charge-based interactions. When administered to animals anticoagulated with enoxaparin, dabigatran, rivaroxaban or apixaban, PER977 was observed to inhibit anticoagulant activity as measured by a variety of assays (thromboelastography, aPTT, anti-Xa) and also reduce the amount of blood lost from standardized wounds. The ability of PER977 to reverse the anticoagulant effect of edoxaban was tested in a phase I clinical study involving 80 healthy volunteers [32]. When PER977 (100 or 300 mg) was administered 3 h after edoxaban (60 mg), whole blood clotting time was reduced to within 10 % of baseline within 10 min. A phase 2 study to evaluate the impact of PER977 treatment on re-anticoagulation with edoxaban is ongoing.

Summary

The TSOACs provide interesting alternatives to the use of the conventional anticoagulants heparin and warfarin. While clinical studies have shown TSOACs to be at least comparable, and sometimes better, in efficacy, they achieve this with some practical benefits including fixed dosing and no need for routine monitoring of drug levels. Although meta-analyses suggest a lower risk for bleeding with TSOAC therapy and similar levels of total bleeding, there will be times when it is desirable or necessary to reverse the anticoagulation produced by TSOACs such as with overdose, traumatic emergencies, or the need for urgent surgery.

Heparin and warfarin target multiple sites in the hemostatic cascade and offer the benefit of specific antagonists—protamine for heparins and vitamin K for warfarin. For the time being, the pendulum has swung in the opposite direction in that while the newer oral anticoagulants are single targeting, the means of reversing their activity has largely encompassed the off-label use of nonspecific pro-hemostatic agents such as PCCs and rFVIIa.

The usefulness of PCCs and rFVIIa at reversing the anticoagulant and/or hemorrhagic effects of TSOAC treatment has been shown on a number of levels. Addition of PCCs to plasma that has been supplemented in vitro with TSOACs reverses the anticoagulant activity. Similar reversals in anticoagulant activity have been observed when blood from animals or healthy humans, who have been anticoagulated with TSOACs, is supplemented ex vivo with PCCs or rFVIIa. The ability of nonspecific reversal agents to reduce hemorrhage has been shown in a variety of animal models that incorporate standardized wounds and in specific models of ICH. One important point to take away from these studies is that reversal of the hemorrhagic effects does not necessarily correlate with reversal of ex vivo anticoagulant activity. In that regard, the mechanism behind the PCC effect is not clear. Several possibilities have been suggested including an enhancement of prothrombinase complex on the platelet surface and an increase in the velocity of thrombin generation [33]. A recent study has demonstrated differential effects of PCC, aPCC, and rFVIIa on clot structure and the rate of fibrin polymerization [11] which may explain some of the differences in the effectiveness of TSOAC reversal that have been observed in earlier studies.

Much less is known about the effectiveness of PCCs and rFVIIa in stopping bleeding in patients

1 Editor's note—Subsequent to the initial preparation of this chapter, Praxbind® (idarucizumab), was approved by the FDA in October 2015 for reversal of dabigatran effect.

treated with TSOACs. Here, the evidence is currently limited to case reports describing experience with a single patient or a small series of patients. Although guidelines have been developed recommending the usage of PCCs and rFVIIa to maintain hemostasis in TSOAC-treated patients presenting with serious or life-threatening bleeding, the variability in outcomes reported in the literature preclude identifying an optimal dosing regimen in terms of which product to use or the dose to treat with. In the reported case studies, the patients described present with different levels of anticoagulation, different comorbid conditions and adjunctive medications and different dosing regimens for the reversal agent(s) used.

The use of the nonspecific reversal agents is also complicated by the need to not tip the hemostatic balance too far in the opposite direction and place the patient in a prothrombotic state, particularly with the use of rFVIIa. Data from animal studies suggests the possibility of "over-correcting" thrombin generation beyond baseline with the use of high doses of PCC, though the impact of such an over-correction on patients has not been defined.

The urgent need for effective TSOAC antagonists is highlighted by the FDA's designation of idarucizumab and andexanet alfa as Breakthrough Therapies. Such a designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. Promising therapies such as these coupled with an enhanced understanding of how PCCs reverse TSOAC-induced anticoagulation are expected to allow for effective treatment of TSOAC-induced hemorrhagic episodes.

References

1. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141:745–52.
2. Flibitte JJ, Hagan N, O'Donnell J, et al. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology. 2004;63:1059–64.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
5. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
6. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
7. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103:1116–27.
8. Stangier J, Rathgen K, Stahle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49:259–68.
9. Singh T, Maw TT, Henry BL, et al. Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. Clin J Am Soc Nephrol. 2013;8(9):1533–9.
10. Chiew AL, Khamoudes D, Chan BS. Use of continuous veno-venous haemodiafiltration therapy in dabigatran overdose. Clin Toxicol. 2014;52(4):283–7.
11. Martin AC, Gouin-Thibault I, Siguret V, et al. Multimodal assessment of non-specific hemostatic agents for apixaban reversal. J Thromb Haemost. 2015;13:426–36.
12. Lambourne MD, Eltringham-Smith LJ, Gataiance S, et al. Prothrombin complex concentrates reduce blood loss in murine coagulopathy induce by warfarin, but not in that induced by dabigatran etexilate. J Thromb Haemost. 2012;10:1830–40.
13. Van Ryn J, Schurer J, Kink-Eiband M, et al. Reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat-tail bleeding model and lack of effect on assays of coagulation. Anesthesiology. 2014;120:1429–40.
14. van Ryn J, Ruehl D, Priepke H, et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. 13th Congress of the European Hematology Association. Copenhagen, Denmark; 2008. p. 148.
15. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. Anesthesiology. 2012;116:94–102.
16. Herzog E, Kaspereit F, Krege W, et al. Correlation of coagulation markers and 4F-PCC-mediated reversal of rivaroxaban in a rabbit model of acute bleeding. Thromb Res. 2015;135:554–60.
17. Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke. 2011;42:3594–9.

18. Zhou W, Zorn M, Nawroth P, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with rivaroxaban. Stroke. 2013;44:771–8.
19. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomized crossover ex vivo study in healthy volunteers. Thromb Haemost. 2012;108:217–24.
20. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573–9.
21. Cheung W, Barco S, Coppens M, et al. In vivo reversal of the anticoagulant effect of rivaroxaban with 4-factor prothrombin complex concentrate. J Am Coll Cardiol. 2014;63(12):A334.
22. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation. 2015;131:82–90.
23. Schulman S, Ritchie B, Goy JK, et al. Activated prothrombin complex concentrate for dabigatran-associated bleeding. Br J Haematol. 2014;164:308–10.
24. Dumkow LE, Voss JR, Peters M, et al. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. Am J Health Syst Pharm. 2012;69(19):1646–50.
25. Vilchez JA, Gallego P, Lip GYH. Safety of new oral anticoagulant drugs: a perspective. Ther Adv Drug Saf. 2014;5(1):8–20.
26. Siegal DM, Garcia DA, Crowther MA. How I treat target-specific oral anticoagulant-associated bleeding. Blood. 2014;123(8):1152–8.
27. Fawole A, Daw HA, Crowther MA. Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban. Cleve Clin J Med. 2013;80(7):443–51.
28. Steiner T, Bohm M, Dichgans M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. Clin Res Cardiol. 2013;102:399–412.
29. Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013;19:446–51.
30. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013;121:3554–62.
31. Grottke O, Honickel M, van Ryn J, et al. A specific antidote to dabigatran reduces blood loss in dabigatran- and trauma-induced bleeding in pigs. J Am Coll Cardiol. 2014;63(12):A295.
32. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med. 2014;371:2141–2.
33. Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent activity. J Thromb Haemost. 2012;10:1478–85.