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Reversal of target-specific oral anticoagulants

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Target-specific oral anticoagulants (TSOACs) provide safe and effective anticoagulation for the prevention and treatment of thrombosis in a variety of clinical settings by interfering with the activity of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban, betrixaban). Although TSOACs have practical advantages over vitamin K antagonists (VKAs), there are currently no antidotes to reverse their anticoagulant effect. Herein we summarize the available evidence for TSOAC reversal using nonspecific and specific reversal agents. We discuss important limitations of existing evidence, which is derived from studies in human volunteers, animal models and *in vitro* experiments. Studies evaluating the safety and efficacy of reversal agents on clinical outcomes such as bleeding and mortality in patients with TSOAC-associated bleeding are needed.

Introduction

Vitamin K antagonists (VKAs) have been the mainstay of long-term antithrombotic therapy for prevention and treatment of thromboembolism. VKAs have practical limitations including long half-lives, drug interactions and unpredictable pharmacokinetics necessitating routine monitoring of anticoagulant effect. Unlike VKAs, which impair the production of vitamin-K-dependent coagulation factors II, VII, IX and X, target-specific oral anticoagulants (TSOACs) exert their anticoagulant effect by inhibiting the activity of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban, betrixaban), coagulation factors that mediate the final stages of coagulation.

TSOACs were developed as alternatives to VKAs owing to practical advantages including rapid onset of action, short half-lives, more-predictable pharmacokinetics, fewer drug interactions and lack of need for routine monitoring. TSOAC drug characteristics are shown in Table 1. Clinical uses of TSOACs include prevention of stroke and systemic embolism in nonvalvular atrial fibrillation, prevention of venous thromboembolism (VTE) following hip and knee arthroplasty and treatment of VTE. Based on large clinical trials and real-world post-marketing surveillance data, TSOACs are at least as effective and safe as VKAs or low molecular weight heparin for approved indications [1–3].

However, unlike VKAs for which vitamin K and coagulation factor replacement with prothrombin complex concentrate (PCC) or plasma can be used to replace coagulation factors and restore coagulation, there are no antidotes available to reverse the anticoagulant effect of TSOACs in the event of bleeding or need for an emergent procedure. Specific reversal agents are currently undergoing clinical development. In this narrative review, we summarize the current published evidence for TSOAC reversal using nonspecific and specific reversal agents.

Types of reversal agents

Coagulation factor replacement

Plasma. Plasma is the aqueous part of blood that contains dissolved proteins including coagulation factors. Plasma transfusion is associated with health risks including transfusion-associated circulatory overload, transfusion-related acute lung injury, allergy and infection [4].

Prothrombin complex concentrates. PCCs are plasma-derived concentrates of vitamin-K-dependent coagulation factors II, IX and X (3-factor PCC; 3-PCC) or factors II, VII, IX and X (4-factor PCC; 4-PCC) with variable amounts of proteins C and S. There is a

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TABLE 1

Pharmacologic properties of target-specific oral anticoagulants.

Target-specific oral anticoagulant	Target	Time to peak concentration (h)	Half-life (h)	Renal excretion
Dabigatran [33,34]	Thrombin	1–3	7–9[a]	80–85%
			7–17[b]	
Rivaroxaban [35–37]	Factor Xa	2–4	7–17[a]	36%
			12–13[c]	
			6–9[b]	
Apixaban [38–40]	Factor Xa	1–3	8–14[a]	25%
Edoxaban [41]	Factor Xa	1–2	6–11[a]	36–45%
			9–10[b]	
Betrixaban [41,42]	Factor Xa	3–4	19	<8%

[a] Healthy adults, single dose.
[b] Healthy adults, multiple doses.
[c] Healthy elderly, single dose.

low risk of viral transmission owing to viral inactivation during product preparation [5]. Thromboembolism is a potential complication of PCC use occurring at a rate of 1.4% when used to treat VKA-associated bleeding [5].

Prohemostatic agents

Activated prothrombin complex concentrate. Activated PCC (aPCC) contains plasma-derived activated forms of coagulation factors II, VII, IX and X. aPCC was developed as a prohemostatic agent to treat bleeding in hemophilia patients with inhibitors to factors VIII or IX [6]. There is a low risk of thromboembolism associated with aPCC use (4–8 events per 10^5 infusions) based on pharmacovigilance data in hemophilia patients [7,8]. However, the majority of these events (81%) occurred in patients with risk factors for thrombosis, which raises concerns regarding aPCC use in patients receiving anticoagulant therapy for prevention or treatment of thrombotic disease.

Recombinant factor VIIa. Recombinant factor VIIa (rVIIa) was also developed as a bypassing agent for bleeding complications in hemophilia patients with inhibitors. Use of rVIIa outside its approved indication is associated with an increased risk of arterial thromboembolism compared with placebo [5.5% *vs* 3.2%; relative risk 1.68; 95% confidence interval (CI) 1.20–2.36] [9].

Specific reversal agents

A humanized monoclonal antibody fragment against dabigatran (anti-Dabi-Fab; Boehringer Ingelheim, Biberach, Germany) is currently undergoing clinical development as a specific reversal agent [10]. It has ~350-fold greater affinity for dabigatran than it does for thrombin, and does not appear to bind endogenous thrombin substrates, activate coagulation or platelets.

A recombinant factor Xa derivative (PRT064445; Portola Pharmaceuticals, San Francisco, CA, USA) is being developed as a specific factor Xa inhibitor reversal agent [11]. The protein lacks catalytic and membrane-binding activity, but retains the ability to bind factor Xa inhibitors with subnanomolar affinity. Also in development is an inactive zymogen-like factor Xa variant, which has demonstrated reversal of the anticoagulant effect of rivaroxaban *in vitro* [12].

PER977 (Perosphere, Bedford, NY, USA) reversed heparin, low molecular weight heparin, fondaparinux, dabigatran, rivaroxaban, apixaban and edoxaban in preclinical studies [13]. The mechanism by which a single molecule could reverse direct and indirect inhibitors of thrombin and factor Xa is not clear and has not been reported.

Evidence for reversal of target-specific oral anticoagulants

Limitations of evidence

Ideally, evidence for reversal would be based on studies of patients with TSOAC-associated bleeding treated with various reversal strategies. Unfortunately, apart from a small number of case reports, such evidence is nonexistent. Instead, current evidence for reversal is limited to studies in human volunteer subjects, animal models and *in vitro* experiments, each of which carries important limitations (Fig. 1).

In vitro investigations comprise the weakest form of evidence for reversal. In these studies, anticoagulated human plasma is spiked with a reversal agent and its effect on a laboratory assay is measured. The major limitation of *in vitro* studies is the use of laboratory test results as a surrogate marker of efficacy as opposed to clinically relevant outcomes such as cessation of bleeding or mortality. Furthermore, widely used tests of coagulation such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) have variable sensitivity and accuracy for measuring the anticoagulant effect of the TSOACs [14].

Evidence for reversal is also derived from animal models in which bleeding is assessed following an induced injury (e.g. tail vein clipping) in the presence or absence of TSOAC treatment. These studies are limited by the need to extrapolate from animals to humans and inherent differences in artificial injury compared with clinical bleeding in patients.

Finally, several studies have been carried out in which healthy volunteers are given a TSOAC and then a reversal agent to measure the effect of the reversal agent on hemostatic laboratory assays. As with *in vitro* experiments, a major shortcoming of these *ex vivo* studies is use of a surrogate laboratory endpoint rather than a clinically relevant outcome. In addition, it is likely that the young