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Review Article

Reversal agents for NOACs: Connecting the dots

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ABSTRACT

Objective: The objective of this review is to provide an overview on the current development of the specific reversal agents for Non-vitamin K Oral Anticoagulants (NOACs).
Methods: We conducted a systematic literature search strategy to identify potential studies on Medline, Embase, and the Cochrane register.
Conclusions: These new reversal agents for NOACs, will help address the unmet need for the management of major or life threatening bleeds, and the management of emergency surgical procedures in patients taking NOACs. It will increase confidence in the use of NOACs; thereby extending treatment to a wider range of patients.

1. Introduction

At present, many Non-vitamin K Oral Anticoagulants (NOACs) have become available for prophylaxis and treatment of venous thromboembolism, and stroke prevention in atrial fibrillation patients as an alternative to vitamin K antagonist (VKAs), such as warfarin and acenocoumarol. Though effective, VKAs pose critical challenges in clinical practice, such as narrow therapeutic index, increased risk of intra cranial hemorrhage (ICH) and slow onset and offset of action, which limits their use in routine practice.[1,2] Large clinical trials evaluating the NOACs across the spectrum of thromboembolic disorders have shown that they are at least as effective as VKAs, with additional benefit of reduced risk of ICH.[3]

An increased risk of bleeding is a known possible complication of all anticoagulant therapies.[4] A meta-analysis by Wang & colleagues suggests that NOACs might be more efficacious and safe in Asians in comparison to non-Asians.[5]

Although the favorable efficacy and safety profile of all NOACs has been demonstrated in the absence of a specific reversal agent,[3] certain clinical situations may arise in which

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Abbreviations: NOAC, Non vitamin K Oral Anticoagulant; VKA, Vitamin K Antagonist; ICH, IntraCranial Hemorrhage; PCC, Prothrombin Complex Concentrate.
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rapid reversal of anticoagulant activity is desirable. Due to the short duration of action of the drugs, the discontinuation of the drug is in most cases sufficient to control the problem. However, need for a reversal agent to neutralize these compounds in case of an overdose or serious bleeding, or when a rapid restoration of hemostasis is required (e.g. perioperative period) has been acknowledged since the clinical use of these anticoagulants began.

Adequate supportive care and temporary removal of all antithrombotic drugs constitute the basis for management of serious bleeding complications associated with NOACs.[6] Pro-hemostatic agents such as 3 or 4 factor prothrombin complex concentrates (PCCs), and activated factor VII have been tried for the NOAC-related bleeding with varying degrees of success.[6] Hemodialysis can remove up to 60% of circulating dabigatran, while administration of activated charcoal may be useful to reduce absorption of dabigatran if taken within 2 h of ingestion and rivaroxaban or apixaban if taken within 6 h after overdose or accidental ingestion.[7–9]

The following reversal agents for NOACs and other anticoagulants are currently in development.

Andexanet alfa (PRT064445) is a modified recombinant derivative of factor Xa under development by Portola Pharmaceuticals, Inc. as a reversal agent for all direct small molecule FXa inhibitors (e.g. rivaroxaban, apixaban, edoxaban, and betrixaban), LMWHs, and fondaparinux.[10]

Ciraparantag (PER977, previously known as aripazine), a synthetic small molecule that binds to FXa inhibitors, dabigatran, and heparins is being developed by Perosphere Inc.[11]

Idarucizumab (BI655075), a humanized mouse monoclonal antibody fragment (FAB), which binds to dabigatran with high affinity (Praxbind Injection, Boehringer Ingelheim Pharmaceuticals, Inc.).

2. Methods

We conducted a systematic literature search strategy to identify potential studies on Medline (1950–present), Embase (1980–present), and the Cochrane register for controlled trials using OVID interface. Publications from potentially relevant journals were also searched by hand.

3. Study selection

Using structured search for idarucizumab (BI655075), andexanet alfa (PRT064445), and ciraparantag (PER977) the studies were selected for this review.

4. The ideal reversal agent to an anticoagulant

The ideal reversal agent to an anticoagulant should be:

- Predictable and efficacious
- Easy to use and with immediate action
- Sustained/Specific/Safe

5. Reversal agents for NOACs

Currently, three reversal agents for NOACs are in clinical development: (1) idarucizumab, (2) andexanet alfa, (3) PER977 (Ciraparantag). Each of these differs in specificity, mechanism of action, and the effect on recognized biomarkers of anticoagulant activity. Table 1 summarizes the pharmacological properties of these reversal agents.

5.1. *Vitamin K*

Vitamin K is frequently and misleadingly named an 'antidote' for the VKAs. An important requirement for an 'reversal agent' is to act rapidly, which is not the case with Vitamin K. When Vitamin K is given to a patient taking a VKA, the liver uses the Vitamin K to start producing fully functioning clotting factors. However, restoring the coagulation factors that require Vitamin K for their production is a slow and complex process with variable effects among patients, which means that the full effect is often not established before 24 h.[12–14]

It is important to remember that warfarin, with its variable half-life of 20–60 h (dependent on individual patient characteristics), still remains in the circulation as an active drug after Vitamin K application. Thus, a re-dosing of Vitamin K may become necessary, depending on the warfarin level and

Table 1 – Pharmacological properties of reversal agents.

	Idarucizumab[17–19]	Andexanet alfa[10]	Aripazine (PER977)[11]
Target	Dabigatran	FXa inhibitors	Universal: FXa inhibitors, dabigatran, and heparins
Mechanism of action	Specific Humanized Fab: specifically binds dabigatran	Non-specific recombinant modified activated FX: competitive affinity for direct FXa inhibitors	Non-specific synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)
Direct prothrombotic signals	Absent	Present (clinically not relevant)	Absent
Administration	IV, bolus or short infusion	IV, bolus and/or continuous infusion	IV
Re-initiate anticoagulation	Possible	No data available	No data available
Inclusion criteria in patient trial	Uncontrolled bleeding or requiring emergency surgery/procedure	Uncontrolled bleeding only	No patient trial yet