Novel Reversal Agents for Non-Vitamin K Oral Anticoagulants

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INTRODUCTION

The drugs that collectively comprise the category of NOACs include dabigatran etexilate (a direct thrombin inhibitor) and rivaroxaban, edoxaban, and apixaban (factor Xa inhibitors). These drugs do not require routine lab monitoring, dietary restrictions, and have a more reliable pharmacokinetic profile. The main clinical concern with these drugs has been the lack of a reversal agent. The following have been investigated for reversal of NOACs:

Prothrombin Complex Concentrate (PCC)

The PCC studied here, Cofact, is an intravenous infusion of the coagulation factors II, VII, IX, X, as well as proteins C, S and antithrombin, all of which are involved in the normal physiologic coagulation process.

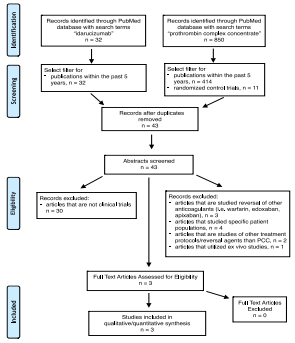
Idarucizumab

This drug is a humanized monoclonal antibody fragment that binds dabigatran etexilate with over 300 times the affinity of thrombin for dabigatran. It is given as an intravenous infusion.

CLINICAL QUESTION

Among male and female patients taking NOACs, is reversal of direct factor XA inhibitors with prothrombin complex concentrate (PCC) more effective than reversal of direct thrombin inhibitors with idarucizumab for cases of major bleeding or requiring emergent or invasive surgery?

METHODS



RESULTS

Study 1: Eerenberg et al.

Objective: Is PCC an effective reversal agent for rivaroxaban and dabigatran?
Study Design: Randomized, double-blind, placebo controlled, crossover phase I clinical trial. Participants included were 12 healthy male paid volunteers ages 20-28 years old.
Results: Before and after PCC IV infusion (mean data values).

	Pre-PCC PT* (s)	Post-PCC PT (s)	Pre-PCC ETP* (%)	Post-PCC ETP(%)
Rivaroxaban	15.8	12.8	51	114
	Pre-PCC aPTT* (s)	**Post-PCC aPTT (s)**	**Pre-PCC ECT* (s)**	**Post-PCC ECT (s)**
Dabigatran	59.4	70.3	69	86

*PT – Prothrombin time ; aPTT – activated partial thromboplastin time ; ECT – Ecarin Clotting time ; ETP – endogenous thrombin potential

Study Critique: Strengths of the study include the simple study design, statistical significance testing and open discussion of the study's limitations. Limitations include a small sample size, healthy participants and financial compensation of volunteers. The study was funded by Sanquin, the producers of Cofact, the PCC used in this study.

Study 2: Glund et al.

Objective: Is Idarucizumab an effective reversal agent for dabigatran?
Study Design: Randomized, double blind, placebo controlled phase 1 clinical trial. Participants included 47 healthy male paid volunteers ages 18 to 45 years old.
Results: Before and 24 hours after idarucizumab IV infusion (mean and median data values).

	dTT* (s)	ECT (s)	Unbound [dabigatran]
Pre-idarucizumab	57	91	137 ng/mL
Post-idarucizumab (4g)	34	37	1 ng/mL

*Dilute thrombin time

Study Critique: Strengths of the study include the use of many coagulation assays to assess reversal. Limitations include no statistical significance testing and a lack of consistency in dosing of dabigatran. The use of study specific upper limits of normal (ULN) for coagulation assays is questionable, as ULN for these assays already exist. The study was funded by Boehringer Ingelheim, the producer of both dabigatran and idarucizumab.

Study 3: Pollack et al.

Objective: Is Idarucizumab an effective reversal agent for dabigatran in clinical practice?
Study Design: Phase III clinical trial with a prospective cohort study design. Participants included 90 patients male and female ages 48 to 93 years old who presented to 184 different sites with either life threatening bleeding or for emergency surgery.
Results: Before and 24 hours after idarucizumab IV infusion (mean and median data values).

	dTT (s)	ECT (s)	Unbound [dabigatran]
Pre-idarucizumab	43.3	76	80.4 ng/mL
Post-Idarucizumab (5g)	30.2	39	1.7 ng/mL

Study Critique: Strengths of the study include the use of a clinically relevant study population and the measurement of total and unbound dabigatran concentrations to correlate with evidence of reversal on coagulation assays. Limitations of the study include a poor presentation of the study's data, lack of statistical significance testing, and unclear reasons for failing to obtain blood samples from patients at designated times.

CONCLUSIONS

Dabigatran reversal as assessed by the ecarin clotting time (ECT)

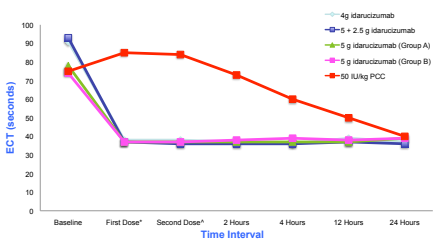


Figure 1: *Data are presented as median values. *4g idarucizumab and 50 IU/kg PCC were given as a single dose. ^5 + 2.5 g and both 5 g doses of idarucizumab were given as 2 separate doses. The 5 g doses were split into 2.5 mg/50 mL infusions.*

- PCC (Cofact) normalized PT and ETP after anticoagulation with rivaroxaban but had no effect on the prolongation of aPTT and ECT after anticoagulation with dabigatran
  - Not currently FDA approved in the U.S.
- Idarucizumab effectively reversed anticoagulation with dabigatran etexilate in 86 percent of participants at 24 hours.
  - FDA approved in October 2015

Concluding statement: Dabigatran etexilate is currently a preferable alternative to rivaroxaban and other factor Xa inhibitors for adults requiring oral anticoagulation because idarucizumab is available for clinical use.

- *Other ongoing clinical trials:* Andexanet alfa, a reversal agent for anticoagulation with factor Xa inhibitors, is currently in phase 4 study and is an FDA-designated breakthrough therapy.

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