Promising Agent Identified as Specific Antidote to Factor Xa Inhibition

Written by Wayne Kuznar

Antidotes to Factor Xa inhibitors are under development and should enhance the safety of the new oral anticoagulant (NOAC) agents, said Richard L. Page, MD, University of Wisconsin–Madison, Madison, Wisconsin, USA.

Reversal of a NOAC is necessary in certain circumstances, such as a spontaneous or provoked hemorrhage (rate of 10% to 20% in Phase 3 trials), an emergency or invasive procedure that requires the rapid reversal of anticoagulation (AC), or serious bleeding in a critical organ.

Reversal options are limited at present, and there is no specific antidote for any NOAC currently. Given this lack of an antidote, the European Working Group on Perioperative Hemostasis issued a set of proposals to evaluate hemostasis in patients treated with rivaroxaban (RIVA) or dabigatran (DABI) prior to surgery [Perod G et al. *Arch Cardiovasc Dis* 2013].

For urgent surgery that has a risk of hemorrhage, a plasma drug concentration ≤30 ng/mL for RIVA or DABI is safe, according to the proposed algorithm based on drug concentrations (Table 1).

Table 1. Algorithm to Assess Safety for Urgent Surgery by NOAC Concentration

Dabigatran
▪ <30 ng/mL: operate
▪ 30–200 ng/mL: repeat level at 12 hours
▪ 200–400 ng/mL: repeat level at 24 hours or dialyze if renal impairment (40–60% reduction within 4 hours)
Rivaroxaban
▪ <30 ng/mL: operate
▪ 30–200 ng/mL: repeat level at 12 hours
▪ 200–400 ng/mL: repeat level at 24 hours; dialysis is not an option

NOAC=new oral anticoagulant.

Adapted from Pernod G et al. *Arch Cardiovasc Dis* 2013.

If drug concentrations are not available, prothrombin time (PT) and partial thromoboplastin time (PTT) are less useful because they do not assess drug concentration or bleeding risk (Table 2). In the case of serious bleeding into a critical organ, the Working Group advises reducing the effect of NOAC therapy by using either activated prothrombin complex concentrate (PCC; 30 to 50 U/kg) or nonactivated PCC (50U/kg) as a first option.

Table 2. Algorithm to Assess Safety for Urgent Surgery When NOAC Concentration Is Unavailable

Urgent Surgery and Rivaroxaban	
There is a worse proposal in case of unavailability of immediate dosage. It does not guarantee the absence of formal hemorrhagic complications.	
Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2	▪ Operate
Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2	▪ Wait up to 12 hours, and obtain specific dosage or new aPTT or PT; *or* (if time is not compatible with emergency): ▪ Operate, if abnormal bleeding: antagonize the anticoagulant effect.
Ratio aPTT > 1.5	▪ Wait up to 12 to 24 hours, and obtain specific dosage, *or* (if time is not compatible with emergency): ▪ Maximum delay surgery ▪ Operate, if abnormal bleeding: antagonize.

NOAC=new oral anticoagulant; aPTT=activated partial thromboplastin time; PT=prothrombin time.

Adapted from Pernod G et al. *Arch Cardiovasc Dis* 2013.

The first antidote to an NOAC under development is the direct reversal agent andexanet alpha, which is a recombinant, modified Factor Xa inhibitor. In describing its action, Dr. Page said that andexanet alpha binds to free Factor Xa inhibitor and allows activated Factor Xa to escape inhibition, thereby converting prothrombin to thrombin to restore coagulation [Ansell J et al. *Nat Med* 2013].

Preclinical data with andexanet alpha show a dose-dependent reversal of RIVA inhibition in a Factor Xa enzyme assay, reversal of the prolongation of the PT produced by RIVA in human plasma, and sustained reversal of whole-blood international normalized ratio values in rats treated with RIVA and other direct Factor Xa inhibitors, as well as mitigation of blood loss in a rabbit liver laceration model [Lu G et al. *Nat Med* 2013].

Clinically, andexanet alpha was able to reverse the AC activity of RIVA in an ongoing Phase 2, double-blind, placebo-controlled study. Data from the first two cohorts (n=18) demonstrated that immediately after dosing, andexanet alpha was associated with a dose-dependent decrease of 32% to 53% in anti–Factor Xa in patients treated with RIVA 20 mg/day for 6 days. On Day 6, andexanet alpha was given intravenously 3 hours after a RIVA dose, and 2 minutes later a dose-dependent reversal of PT and clotting factor was observed. Activity of the tissue factor pathway inhibitor was decreased as expected, due to its binding to andexanet alpha. The direct reversal agent andexanet alpha was well tolerated, without the occurrence of thrombotic events or serious adverse events.