

## **A Closer Look at the Perioperative Care PRN**

### Overview

The American College of Clinical Pharmacy Practice and Research Networks (ACCP PRNs) were created to allow professional interaction between pharmacists, residents, and students with similar interests, backgrounds, and experience. The Perioperative Care PRN was established in 2014 to provide education and resources related to the overall management of perioperative patients, address the regulatory requirements imposed by accrediting bodies, and provide a place for members to discuss complicated perioperative patients and seek input and recommendations on care.

The ACCP Perioperative Care PRN strives to address common concerns associated with pre-, inter-, and postoperative phases of care as they relate to patient-specific parameters (age, sex, and comorbid conditions) and medical severity. The scope of this network includes addressing underlying disease processes and progression, successfully managing sedation and pain, identifying alterations in drug disposition (administration, absorption, distribution, metabolism, and excretion), and using evidence-based medicine to evaluate and minimize surgical complications. The goal of this network is to incorporate interdisciplinary collaboration through academia, research, and practice development while ensuring the safe and effective perioperative management of all patient populations.

### Opportunities

Resident and fellow members have the ability to interact through the e-mail list, the ACCP Perioperative Care PRN Facebook group (<https://www.facebook.com/#!/groups/742181659164330/>), and the PRN business meeting and focus session at the 2015 Global Conference in San Francisco, California. In addition, this new Perioperative Care PRN intends to maximize its benefit to its members through several other avenues. Future endeavors include developing joint-PRN focus sessions with one or more of the current PRNs, establishing a member award and a travel award, creating a biannual PRN newsletter that includes highlights of member activities, and collaborating on the development of guidelines or position statements related to perioperative care.

### Clinical Issue

The care of the perioperative patient encompasses a wide range of disease states and severity of illness levels. Patients with blood disorders are at an increased risk of perioperative complications throughout the transitions of care and surgical spectrum. Pharmacists involved in the management of perioperative patients must examine underlying disease processes, acute pain management, anesthesia risks, alterations in drug disposition, and potential long-term complexities.

Given the recent increase in the use of novel oral anticoagulants (NOACs) as an alternative to the vitamin K antagonists, the comorbidities of surgical patients, and the prevalence of postoperative bleeding and clotting complications, pharmacists can be proven assets to the surgical team by staying up to date with the literature surrounding the development and availability of the reversal agents for this new class of anticoagulants. Below is a synopsis of the pipeline reversal drugs, hyperlinks to articles, and a table for quick reference:

#### 1. ACCP Perioperative Care PRN

- (1) **Andexanet alfa:** A reversal agent for anti-factor Xa (anti-Xa) drugs such as rivaroxaban, apixaban, and edoxaban,<sup>1</sup> andexanet alfa was well tolerated in the ANNEXA-A part 1 study. No thrombotic events or adverse effect from treatment was seen, and all andexanet subjects achieved 90% or greater reversal. Effect of treatment lasted 1–2 hours after bolus administration. Andexanet alfa was also well tolerated and showed immediate and significant reversal of rivaroxaban in the randomized, double-blind, placebo-controlled phase III ANNEXA-R study.<sup>2</sup> In animal models, the investigators noted up to an 85% reduction in blood loss within 2 hours of andexanet alfa administration.<sup>3</sup>
- (2) **Idarucizumab:** An antidote for dabigatran,<sup>4</sup> idarucizumab showed normal clotting during surgery in 92% of patients during the RE-VERSE AD trial and showed no signs of procoagulant effect after drug use and reversal.<sup>5</sup>
- (3) **Aripazine:** A nonspecific antidote that binds to IIa and Xa,<sup>6</sup> aripazine has shown a decrease in blood loss in animal models because of its ability to restore clot integrity. Research in human subjects is ongoing.<sup>7</sup>

Table 1.

<b>Andexanet (PRT064445)<sup>1-3</sup></b>	<b>Idarucizumab (aDabi-Fab/BI 655075)<sup>4,5</sup></b>	<b>Aripazine (PER977)<sup>6,7</sup></b>
Reversal agent for anti-Xa drugs such as rivaroxaban, edoxaban, and apixaban	Antidote for dabigatran	A nonspecific antidote that binds to IIa and Xa
<b>MOA:</b> Competes with circulating levels of factor Xa; inhibits direct and indirect factor Xa-mediated anticoagulation by binding directly to the factor Xa inhibitors and heparin-antithrombin complexes <sup>1-3</sup>	<b>MOA:</b> Monoclonal antibody fragment that binds free and thrombin-bound dabigatran and neutralizes dabigatran's effects <sup>4</sup>	<b>MOA:</b> Binds to IIa and Xa (NOACs, UFH, LMWH, and fondaparinux) by hydrogen bonding <sup>6</sup>
<b>ANNEXA-A DOSE (phase III)<sup>1</sup>:</b> <b>Part 1:</b> 400 mg of andexanet IV bolus to reverse apixaban <b>Part 2:</b> Andexanet 400 mg IV bolus + andexanet IV continuous infusion of 4 mg/min <b>ANNEXA-R DOSE (phase III):</b> <b>Part 1:</b> Volunteers were given rivaroxaban 20 mg PO qday for 4 days and received either andexanet alfa 800 mg IV bolus or placebo <b>Part 2:</b> Rivaroxaban 20 mg PO qday for 4 days and either andexanet alfa 800 mg IV bolus followed by andexanet alfa IV continuous infusion at a rate of 8 mg/min for 120 min or placebo <sup>2</sup>	<b>RE-VERSE AD DOSE (phase III):</b> 5 g of IV idarucizumab administered as two 50-mL bolus infusions of 2.5 g of idarucizumab given 15 min apart; dabigatran doses generally were 75 mg, 110 mg, or 150 mg PO BID <sup>4</sup>	<b>DOSE:</b> Still in early-phase trials; 1 hr after aripazine 100-mg IV dose, edoxaban 60 mg was reversed; does not appear to have procoagulant properties <sup>6</sup>
<b>ANNEXA-A preliminary results:</b> No thrombotic events or adverse effect from treatment. All andexanet	<b>Interim analysis results:</b> 90 patients with a median age of 76.5 yr were enrolled. The	<b>Results:</b> Has been shown to decrease blood loss in animal models because of its ability to

<p>subjects achieved <math>\geq 90\%</math> reversal. Effect of treatment lasted 1–2 hr after bolus administration<sup>1</sup></p> <p><b>ANNEXA-R preliminary results:</b> The treatment dose in the first part of the ANNEXA-R study was well tolerated and showed immediate and significant reversal of rivaroxaban. The second part of the ANNEXA-R study is ongoing<sup>2</sup></p>	<p>treatment showed normal clotting during surgery in 92% of patients and showed no signs of procoagulant effect after drug use and reversal<sup>4</sup></p>	<p>restore clot integrity.<sup>6</sup> Research in human subjects is ongoing; appears to decrease clotting time in healthy volunteers who received edoxaban followed by aripazine<sup>7</sup></p>
---	--	---

BID = twice daily; IV = intravenous(ly); LMWH = low-molecular-weight heparin; MOA = mechanism of action; NOAC = novel oral anticoagulant; PO = oral(ly) q = every; UFH = unfractionated heparin.

The days ahead are exciting for pharmaceutical discovery and research, which will help improve patient safety and survival in patients requiring urgent reversal of the new oral anticoagulants. For more information about these reversal agents and their management, please join us at our inaugural Perioperative Care PRN focus session at the ACCP 2015 Global Conference. Experts in the field will also discuss anticoagulant considerations with neuraxial anesthesia and the surgical care of patients with hemophilia. Please see <https://www.accp.com/meetings/gc15/schedule.aspx?mode=detail&i=4850> for more details.

## References

1. Crowther M, Levy G, Lu G, et al. ANNEXA-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Apixaban-Induced Anticoagulation in Older Subjects by Andexanet Alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors. Available at [https://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm\\_469639.pdf](https://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469639.pdf). Accessed August 5, 2015.
2. Portola Announces Phase 3 ANNEXA-R Study of Andexanet Alfa and Factor Xa Inhibitor XARELTO (rivaroxaban) Met Primary Endpoint with High Statistical Significance. Andexanet Alfa is the Only Universal Factor Xa Inhibitor Antidote Shown to Directly Reverse the Anticoagulant Activity of These Agents in Clinical Studies. Portola Pharmaceuticals. January 9, 2015. Available at <http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=2005429>. Accessed August 5, 2015.
3. Lee W, Patel DV, Lisi DL. Reversal of Novel Oral Anticoagulants. Available at [www.uspharmacist.com/content/c/53083/](http://www.uspharmacist.com/content/c/53083/). Accessed August 5, 2015.
4. Pollack CV, Reilly, PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-20. Available at [www.nejm.org/doi/full/10.1056/NEJMoa1502000](http://www.nejm.org/doi/full/10.1056/NEJMoa1502000). Accessed August 6, 2015.
5. Idarucizumab Reverses the Anticoagulant Effect of Dabigatran Within Minutes in Patient Study. Boehringer Ingelheim. June 22, 2015. Available at [www.boehringer-ingelheim.com/news/news\\_releases/press\\_releases/2015/22\\_june\\_2015\\_dabigatranetexilate.html](http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/22_june_2015_dabigatranetexilate.html). Accessed August 5, 2015.
6. Costin JC. PER977 [aripazine] - A Non Specific Anticoagulant Reversal Agent. Perosphere. April 22, 2014. Available at [http://cardiac-safety.org/wp-content/uploads/2014/11/3.-James-Costin\\_Perosphere.pdf](http://cardiac-safety.org/wp-content/uploads/2014/11/3.-James-Costin_Perosphere.pdf). Accessed August 5, 2015.
3. ACCP Perioperative Care PRN

7.Moll S. Antidotes for the New Oral Anticoagulants: Update. ClotConnect.org. Available at <http://professionalsblog.clotconnect.org/2014/11/07/antidotes-for-the-new-oral-anticoagulants-update-2/>. Accessed August 5, 2015.

Submitted by:

Stacey Bortlik (Moultrie), Pharm.D., BPharm, C.Ph., R.Ph., PRS  
Chair, ACCP Perioperative Care Practice and Research Network  
Pediatric Clinical Pharmacist, UF Health Shands Hospital  
Clinical Assistant Professor and Portfolio Mentor, UF College of Pharmacy  
Gainesville, Florida

4. ACCP Perioperative Care PRN