ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 19 - ISSUE 3 - AUTUMN 2019

SPECIAL SUPPLEMENTS

CSL Behring Symposium Report

Factor Concentrates in the Perioperative Management of Coagulopathy

Nestlé Nutrition Institute Symposium Report

The Expanding Boundaries of ICU Nutrition

Nutrition

New ESPEN Guidelines for Nutrition in the Critically Ill: Help, What Happened!? *M. Casaer, G. Van den Berghe, J. Gunst*

New Trends in ICU Nutrition, *V. Fraipont, J.C. Preiser*

Emerging Concepts in Nutritional Therapy for the Critically Ill Child, *N. Mehta*

Obesity and Nutrition in Critical Illness, *E. Ridley, M. Chapman, K. Lambell, S. Peake*

Objective Malnutrition Diagnosis and Personalised Nutrition Delivery in the ICU, *P. Wischmeyer, J. Molinger*

The Role of Speech and Language Therapy Supporting Nutritional Management in ICU, *J. McRae*

PLUS

Virtual Reality in the Intensive Care Unit: State of Play and Future Prospects, *V. Beaucote, O. Clovet, A. Esnault, T. Lescot*

Pre-packed Critical Care Drug Pouch for Acute Patient Care: Consensus, Simulation Testing and Recommendations, *A. Gandhi, W. Chan, C. Meyers, P. Barach, F. Rubulotta*

Knowledge Transfer to Improve Outcomes in Critically Ill Immunocompromised Patients, *E. Azoulay*

Challenges in the Management of the Critically Ill Patient, *M. Antonelli*

09

9 771377 756005

Jerrold Levy
Professor of Anesthesiology
Professor of Surgery (Cardiothoracic)
Co-Director, Cardiothoracic ICU
Duke University School of Medicine
Durham, North Carolina
USA

jerrold.levy@duke.edu

@JerroldLevy

Treatment Options for Factor-Xa Inhibitor-Related Bleeding

Specific treatment options for factor Xa inhibitor-related bleeding, focusing on drugs like rivaroxaban, apixaban, and edoxaban.

Non-vitamin K oral anticoagulants (NOACs/DOACs) are direct reversible inhibitors of factor Xa. These drugs are also reversible inhibitors versus warfarin or other vitamin K antagonist that are used in Europe. Anticoagulants decrease circulating levels of factor II, VII, IX and X. In patients with acute bleeding, the concept of factor concentrates is to restore the levels of these agents. When a patient comes in on a NOAC and needs emergency surgery or is actively bleeding, two important questions must be asked. One is what's their renal function as it can have an impact on drug elimination, and the other is coagulation testing.

Measuring the effects of these new oral anticoagulants and nonvitamin K can be confusing for clinicians. There are some important caveats to consider (Heidbuchel H et al. 2013):

- Prothrombin time (PT)/ International normalised ratio (INR)/partial thromboplastin time (PTT) are relatively insensitive to the effects of anti-FXa agents and are reagent-dependent
- Normal PT and PTT do not rule out significant blood level of DOACs, especially anti-FXa agents
- In case of elevated PT, this may represent high blood levels of DOACs or coagulopathy

With respect to when to decide to potentially consider drug levels, it should be done:

- o If the patient is bleeding or there is a risk of potential overdose
- o In case of impaired renal or liver function
- o To evaluate for low level prior to surgery

Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical. The two specific state of the art reversal agents (also called antidotes) that can be used to manage a major bleed include idarucizumab and andexanet. Andexanet reverses FXa inhibitors. Once bound to andexanet, inhibitors are unable to bind/inhibit FXa (Ansell 2013). Andexanet comes in vials that require mixing, and is given as a loading dose followed by an infusion of two hours. The drug effect on reversal is about three hours (**Figure 1**). A large study was conducted, which led to the drug's approval both in the U.S. and in Europe. However, it is important to note that there is no current surgical data supporting this particular use. The drug is approved for emergency medical bleeds only, in particular, intracranial haemorrhages. Of the 352 patients in the final New England Journal of Medicine study, 64% were intracranial hemorrhage, and about 26% were GI bleeds.

> **bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy**

As demonstrated in **Figure 2**, anti–factor Xa activity among persons who had received anticoagulation treatment with apixaban or rivaroxaban was measured before and after the administration of andexanet or placebo on study day 4. Dashed lines indicate the end of administration of the bolus or infusion. Panel A shows data from participants in the apixaban study (ANNEXA-A) who received andexanet, as a 400-mg intravenous bolus, or placebo; Panel B participants in the rivaroxaban study (ANNEXA-R) who received andexanet, as an 800-mg intravenous bolus, or placebo; Panel

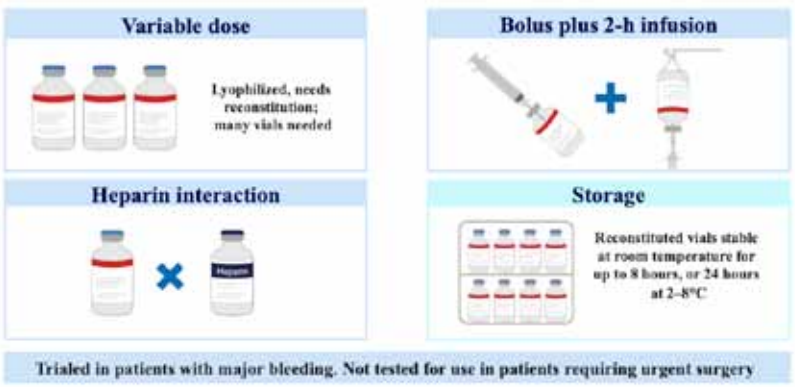

Figure 1. Andexanet Rx: IV load + infusion (Levy et al. 2018)

C participants in the apixaban study who received andexanet, as a 400-mg intravenous bolus plus a 4-mg-per-minute infusion for 120 minutes, or placebo; and Panel D participants in the rivaroxaban study who received andexanet, as an 800-mg intravenous bolus plus a 8-mg-per-minute infusion for 120 minutes, or placebo. Different scales along the x axis in each graph are used to enable visualisation of the immediate, short-term dynamics as well as the longer-term dynamics of anti–factor Xa activity after andexanet treatment. The points on the graph represent the mean anti–factor Xa activity level, and I bars indicate the standard error. There was a significant difference ($P<0.05$) in the percent change in anti–factor Xa activity (relative to the pre-bolus activity level) between andexanet and placebo until 2 hours after administration of the bolus or infusion (Siegel et al. 2015).

As far as the use of prothrombin complex concentrates (PCC) is concerned, they have the potential to treat bleeding, but there is a lack of correlation between laboratory tests and bleeding or treat of anticoagulation. PCCs are used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation (Zahir et al. 2014; Dickneite et al. 2014; Heidbuchel et al. 2015; Levy et al. 2014; Weitz et al. 2015; Levi et al. 2014; Brown et al. 2016).

One of the most important things to remember is that bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy. PCCs and other factor concentrates should be part of this multi-modal strategy.

With respect to managing bleeding with DOACs, some important factors to consider and certain important elements to remember:

- How urgent/emergent is the bleeding
- Whether there is time to decide if drug levels are contributing
- Whether the patient needs procedural intervention for the bleed
- Standard coagulation tests should be performed with bleeding and followed
- Reversal strategies are part of a multi-modal strategy in addition to fixing the bleeding lesion
- Reversal agents will only remove the role of the anticoagulant
- Identify and take out the source while minimising the amount of blood loss
- Critically ill patients require haemodynamic and haemostatic resuscitation

Finally, it is important to develop institution-wide protocols for emergencies. Also, it must be noted that reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at great risk for adverse outcomes (Crowther et al. 2016). ■

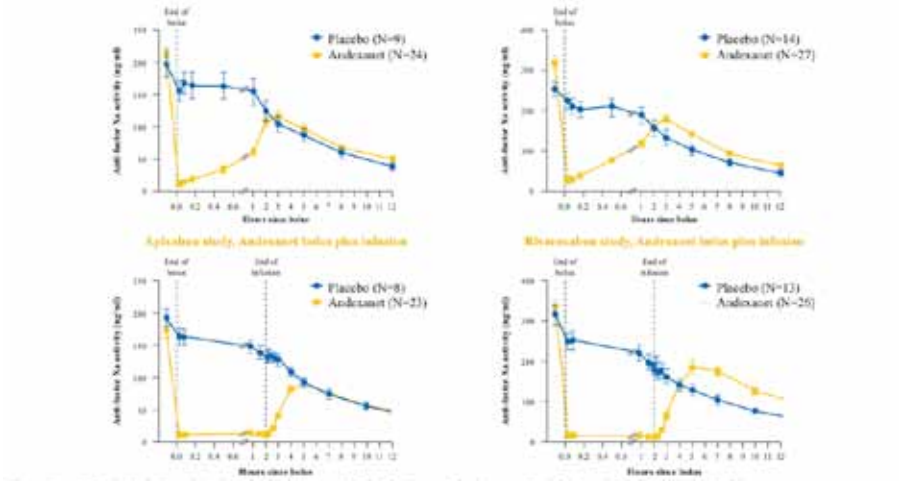

Figure 2. Time courses of anti–factor Xa activity before and after administration of andexanet (Siegel et al. 2015). Reprinted with permission from Massachusetts Medical Society

Key Points

- Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical.
- Two of the state of the art reversal agents that can be used to manage a major bleed include idarucizumab and andexanet.
- PCCs can be used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation.
- Reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at greak risk for adverse outcomes.

Abbreviations

NOAC	non-vitamin K oral anticoagulants
DOAC	direct oral anticoagulants
INR	international normalised ratio
PCC	prothrombin complex concentrates
PT	prothrombin time
PTT	partial thromboplastin time

References

Bilecen S, de Groot JA, Kalkman CJ, Spanjersberg AJ, Brandon Bravo Ansell JE (2013) Blocking bleeding: reversing anticoagulant therapy. Nat Med,19:402–4.

Brown KS (2016) Non VKA oral anticoagulant activity: challenges in measurement and reversal. Crit Care, 20:273.

Crowther M, Crowther MA (2015) Antidotes for novel oral anticoagulants: current status and future potential. Arterioscler Thromb Vasc Biol, 35:1736–45.

Dickneite G, Hoffman M (2014) Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence? Thromb Haemost, 111:189–98.

Heidbuchel H et al. (2015) Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace, 17:1467–507.

Levi M et al. (2014) Comparison of 3-factor and 4-factor PCCs for reversal of the anticoagulant effects of RIVA in volunteers. J Thromb Haemost, 12:1428–36.

Levy JH et al. (2018) Rivaroxaban reversal with PCC or tranexamic acid in healthy volunteers. J Thromb Haemost,16:54–64.

Siegal DM et al. (2015) Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. New Engl J Med, 373, 2413–24.

Weitz JI, Pollack CV (2015) Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. Thromb Haemost, 114:1113–26.

Zahir H et al. (2015) Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor PCC. Circulation, 131:82–90.