Letter to the Editor

Antidotes for patients taking novel oral anti-coagulants

Dear Sir:

Novel oral anti-coagulants [NOACs: dabigatran (Pradaxa[®], Boehringer Ingelheim, Germany), rivaroxaban (Xarelto[®], Bayer, Germany), apixaban (Eliquis[®], Bristol-Myers Squibb, USA), edoxaban (Savaysa[®], Daiichi-Sankyo, Japan)] are used more often for the prevention of systemic embolism in atrial fibrillation and for the treatment of venous thromboembolism. Unlike warfarin, NOACs have more predictable pharmacokinetics, fewer drug interactions, shorter half-lives, and quicker onset of action.^[1] They do not require frequent laboratory monitoring, but there is a lack of validated reversal strategies for these agents in cases of emergency surgery, life-threatening bleeding, and overdose.^[2] Elderly patients with impaired renal function are especially vulnerable.

NOACs are classified into two groups: direct thrombin inhibitor (notably dabigatran) or factor Xa inhibitors (including rivaroxaban, apixaban, and edoxaban). As factor Xa catalyzes the activation of prothrombin into thrombin, all NOACs exert an anti-thrombin effect and prevent activation of fibrinogen into fibrin. Ideally, NOACs should be stopped 18–48 hours before non-lifesaving elective surgery and resumed 6–72 hours post-operatively.^[3] As all NOACs have short half-lives, it is recommended to delay non-life threatening surgery until the effects have worn off. Bridging anticoagulation is usually not necessary because of their short half-lives.^[4]

In the emergency setting, multidisciplinary discussion with hematologists, cardiologists, intensive care specialists, and anesthesiologists is mandatory. It is often feared that for patients with major bleeding, an inability to rapidly reverse the anticoagulant effects of NOAC may seriously compromise the clinical outcome and even render the situation unsalvageable. The activated partial thromboplastin time (APTT) and prothrombin time (PT) do not exhibit a linear relationship with NOACs' anticoagulant effects.^[2] Instead, the only accurate means to gauge NOACs' activity and plasma drug level is through specific clotting assays: diluted thrombin time assay (dTT) for dabigatran and drug-specific anti-Xa chromogenic assay for factor Xa inhibitors.^[3] At the moment, these assays are not available in most hospitals. Only dabigatran's absorption has been shown to be reduced by activated charcoal, while rivaroxaban is not,

and the effect is unclear for abixaban and edoxaban. Hemodialysis is only effective in eliminating dabigatran as this is bound to 35% of plasma proteins, in contrast to the factor Xa inhibitors, which exhibit plasma protein-bound fractions in excess of 85%.^[2]

In the event of life-threatening hemorrhage, replenishment of clotting factors through off-label use of prothrombin complex concentrate (Kcentra[®], CSL Behring, Germany which contains factors II, VII, IX, X, protein C and protein S),^[5] activated prothrombin complex concentrate (Factor Eight Inhibitor Bypassing Activity[®], Baxter, USA), or recombinant-activated factor VIIa (Novoseven[®], Novo Nordisk, USA) may be considered.^[6] However, the effectiveness of prothrombin complex concentrate or activated prothrombin complex concentrate is not demonstrated in clinical trials and because of conflicting data, no consensus is available for treatment protocols or dosage.

The call for a clinical antidote to NOAC is thus urgent. Ongoing clinical trials demonstrated promising results for specific antidotes that directly neutralized the actions of NOACs: idarucizumab (Boehringer Ingelheim, Germany) for dabigatran, andexanet-alfa (Portola, USA) for factor Xa inhibitors, and aripazine (Perosphere, USA) as a universal NOAC antidote. Idarucizumab is a monoclonal antibody fragment that binds to dabigatran with 350 times higher affinity than thrombin, thereby preventing dabigatran from inactivating thrombin.^[2] Phase I clinical trials in the United States demonstrated immediate and complete reversal of dabigatran's effects, with sustained action for more than 12 hours after 4 g of intravenous idarucizumab was given in all three groups of patients: middle-aged, elderly, and renal-impaired.^[6] As the kidneys are responsible for 80% of dabigatran's excretion,^[3] this illustrates how idarucizumab is effective even in those with chronic renal insufficiency.

An intravenous antidote that is effective against all factor Xa inhibitors is andexanet-alfa, a modified recombinant factor Xa that binds avidly to rivaroxaban, apixaban, and edoxaban. Recently, the ANNEXA-A Study, a phase 3, randomized, double-blind, placebo-controlled trial that assessed the use of andexanet-alfa for the reversal of apixaban-induced anticoagulation in older patients involving 34 participants aged 50 to 75 years

who were randomly assigned at a 3:1 ratio to andexanet-alfa ($n=24$) or placebo ($n=9$) with all participants received apixaban 5 mg twice daily for 4 days showed that a single intravenous 400 mg bolus of andexanet-alfa induced prompt and complete dose-dependent reversal of rivaroxaban and apixaban in phase 1 and 2 studies in the United States.^[7]

Aripazine (also known as PER977) is a universal NOAC antidote that binds to both factor Xa inhibitors and dabigatran through hydrogen bonds. Aripazine completely reversed the anticoagulant effects of dabigatran, rivaroxaban, and apixaban in ex-vivo human plasma studies.^[2] This is corroborated by recently released phase 1 study results on edoxaban-treated subjects, showing total return to baseline hemostasis, indicated by whole-blood clotting time, 10–30 minutes after a single intravenous dose of aripazine.^[8] The reversal was sustained for 24 hours without any increase in pro-coagulant activity, although some subjects reported transient peri-oral and facial flushing. Phase 2 trials for aripazine are ongoing.

With a growing number of patients taking NOACs, physicians should be equipped with the knowledge on their pharmacology and ways to counteract their effects in emergency. In order to support the widespread international clinical application of NOACs, blood tests on their efficacy and antidotes ought to become readily available, as it is anticipated that NOACs may herald the dawn of a new era in anticoagulation where stringent dietary restrictions and tedious monitoring soon would become recollections of the past. The most important final message is that despite the soon available antidotes, the priority in the acute settings should be the continual clinical evaluation of the patient, to review the indication for the NOAC, and the timing of the last dosage, so as to determine whether reversal of the anticoagulation is required. These antidotes are likely to be very costly, and sometimes, watchful waiting in addition to resuscitatory or supportive measures may be adequate.

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World J Emerg Med 2015;6(4):311–312

DOI: 10.5847/wjem.j.1920–8642.2015.04.012

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Received May 12, 2015

Accepted after revision September 20, 2015