Reversal of new oral anticoagulants and personalized medicine

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Given that innovation is a way of life, researchers constantly strive to develop new anticoagulants and their antagonists, sometimes being unaware of their necessity, effectiveness and cost. Scientists are fascinated by new anticoagulants and their reversal agents. Despite their enormous costs and difficulty in monitoring, we somehow tend to prefer the new oral anticoagulant drugs just because they are new and have been found to be noninferior over warfarin in clinical trials.

Unfractionated heparin, a parenteral anticoagulant, and warfarin, an oral anticoagulant, have been conventionally used as anticoagulants. Heparin is effectively monitored by activated partial thromboplastin time (APTT) and the success of heparin use lies in the availability of protamine sulfate as an effective antidote. Warfarin, on the other hand, is effectively monitored by prothrombin time/international normalized ratio (PT/INR) and relies on the availability of vitamin K as its most effective antagonist. There have been newer strides with the development and approval of low-molecular-weight heparins but so far there are no effective specific antagonists, but rather there is reliance on protamine sulfate which is only partially effective.

Nonvitamin k antagonist oral anticoagulants

As we commemorate 100 years of the use of heparin and more than 50 years of use of

warfarin, four new nonvitamin K antagonist oral anticoagulants (NOACs) have been approved by the US FDA since 2010. One among them is a thrombin inhibitor (dabigatran) while the other three are factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). A fourth factor Xa inhibitor, betrixaban, which has a lower renal clearance and hepatic metabolism and a longer half-life compared with approved NOACs, is in clinical development [1,2]. Although NOACs have decreased bleeding risk with noninferior efficacy when compared with warfarin in patients with atrial fibrillation [3–7], an effective and specific antagonist is still absolutely necessary. While nonspecific hemostatic agents such as prothrombin complex concentrates (PCCs), activated PCCs and recombinant factor VIIa may be used, more specific options are desirable. One such specific agent is the approved humanized monoclonal antibody fragment, idarucizumab, which is used as a reversal agent for dabigatran. The investigational factor Xa decoy andexanet alfa and the synthetic, small molecule, ciraparantag, may reverse the anticoagulant effects of factor Xa inhibitors.

All anticoagulants cause bleeding. The success of any anticoagulant besides its safety and efficacy is dependent on the availability of a specific, safe and effective antagonist. Heparin and warfarin serve as examples whose anticoagulant effects can be easily reversed. During scenarios such as serious

Omer Iqbal

Author for correspondence:
Department Pathology
& Ophthalmology, Loyola
University Medical Center,
Maywood, IL 60153, USA
oiqbal@luc.edu

Walter Jeske

Department of Thoracic
& Cardiovascular Surgery
& Pathology, Loyola
University Medical Center,
Maywood, IL 60153, USA

Jawed Fareed

Department Pathology
& Pharmacology, Loyola
University Medical Center,
Maywood, IL 60153, USA

bleeding or the need for emergency surgery, a physician needs to know the circulating concentration of the drug or the residual anticoagulant activity. For dabigatran, given that most institutions are not adept at measuring the serum concentration of dabigatran, one has to be content with tests such as the activated partial thromboplastin time or the too sensitive dilute thrombin time and the generally unavailable ecarin clotting time tests. In the case of factor Xa inhibitors, physicians must rely on highly variable prothrombin time or the too sensitive and often clinically unavailable anti-Xa assays. The recommended chromogenic anti-Xa assays still need validation and have a delayed turnaround time, making them impractical in emergency settings.

Reversing the effects of NOACs

The areas of uncertainty in the management of NOACs are perioperative management, laboratory monitoring of anticoagulation and management of bleeding complications. During the management of periprocedural anticoagulation with NOACs, both the risks of bleeding and thrombosis should be evaluated and the decision to cease the NOAC should be individualized or personalized [7]. Due to a lack of specific tests, the monitoring issues in assessing the residual activity become compounded both before and after using either the nonspecific hemostatic agents or the specific NOAC reversal agents. The nonspecific hemostatic strategies include alteration of pharmacokinetics of NOACs, antifibrinolytic drugs, PCCs, activated PCCs, factor eight bypassing activity, recombinant factor VIIa, cryoprecipitates and fresh frozen plasma. While fresh frozen plasma should not be used to reverse the anticoagulant effects of NOACs because of its limited effectiveness by virtue of lower concentrations of clotting factors and the potential for heart failure due to volume overload [8], the other nonspecific agents are equally impractical due to their variable efficacy [9,10]. While the absorption of dabigatran can be reduced by the administration of activated charcoal, the absorption of rivaroxaban is unaffected. It is unclear whether the absorption of apixaban and edoxaban can be modified by the administration of activated charcoal. Dabigatran, due to its low binding of plasma proteins, could be eliminated from the circulation by performing hemodialysis. Since factor Xa inhibitors have higher binding to plasma protein fractions, they are not effectively eliminated by hemodialysis. With regard to the specific reversal agents, Idarucizumab was initially granted priority review by the FDA in order to accelerate its approval. Following its approval in October 2015, there have been at least four critically ill patients with dabigatran-induced bleeding who failed to reach

effective hemostasis with idarucizumab [11–14]. In addition to these four cases, the real world data will eventually prove the degree of validity of idarucizumab as an antidote for dabigatran. Andexanet alfa was evaluated in Phase III ANNEXA (andexanet alfa, a novel antidote to anticoagulant effects of factor Xa inhibitors) which studies to test its safety and efficacy in healthy subjects anticoagulated with apixaban (ANNEXA A) and rivaroxaban (ANNEXA-R). However, the FDA is yet to approve andexanet alfa to reverse the effects of direct and indirect FXa inhibitors [15]. Ciraparan-tag/PER977, a small synthetic cationic molecule that binds direct FXa inhibitors, direct thrombin inhibitors, unfractionated heparin, low-molecular-weight heparin through noncovalent hydrogen bonds and charge–charge interactions, is in clinical development albeit it has the potential to cause platelet activation [7].

New oral anticoagulants & platelet aggregation inhibitors

Platelet activation and platelet reactivity may pose a prothrombotic challenge in the management of patients who are receiving a combination therapy comprising antiplatelet and new oral anticoagulants and who require reversal agents to neutralize the anticoagulant effects. Patients on clopidogrel, a P2Y₁₂ inhibitor which is activated by the CYP450 system and who carry the *CYP2C19**2 allele, metabolize clopidogrel poorly and may be at a higher risk of thrombosis, especially when their concomitant new oral anticoagulant drugs are being antagonized by reversal agents for bleeding complications. Platelet hyper-reactivity may result in initial and recurrent arterial thrombosis [16]. Albeit newer P2Y₁₂ inhibitors are increasingly becoming available, clopidogrel is still widely used. Voraxapar, a platelet PAR-1 antagonist was recently approved by the FDA. Common variants in the human platelet PAR-4 thrombin receptor are reported to alter platelet function and differ by race [17]. This could be significant in clinical scenarios where patients are concomitantly placed on voraxapar and new oral anticoagulant drugs, and require reversal agents to neutralize the anticoagulant effects.

Despite drug manufacturers' claims that a particular reversal agent does not have procoagulant effects upon neutralizing NOACs, there may still be chances of triggering of procoagulant effects due to the presence of any inherited or acquired thrombotic disorders. Since screening of patients for such disorders is not feasible each time a reversal agent is given, one cannot discount the possibility that a procoagulant or hypercoagulant response will not be triggered. The real world data on reversal agents will shed more light on the imminent adverse outcomes. Further-

more, in some other scenarios where a combination of NOAC, antiplatelet and fibrinolytic is onboard, reversal of NOACs alone may not be sufficient and since the effects of other drugs are not counteracted, there could be adverse bleeding effects despite reversal agents. As these critical scenarios happen in emergency situations, these adverse outcomes may be unavoidable.

Conclusion

The concept of personalized medicine actually originated in India more than 5000 years ago, when Ayurveda, a natural healthcare system emphasized the treatment of disease in highly individualized manner and was best summed up at that time in a quotation by Charaka Samhita, “Every individual is different from another and hence should be considered as a different entity. As many variations are there in the universe, all are seen in human beings” [18].

All anticoagulant drugs have the potential to cause bleeding complications. In order to prevent bleeding or

thrombotic complications, the doses of NOACs need to be calibrated or individualized in addition to the availability of better tests to effectively monitor them. Furthermore, in order to prevent thrombotic complications in patients who are on reversal agents to neutralize the anticoagulant effects of NOACs, the doses of reversal agents also need to be calibrated or individualized. In other words, the concepts of personalized or precision medicine need to be increasingly incorporated in the routine management of patients in order to achieve better clinical outcomes.

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