Review

Eurasian Journal of Toxicology

An Overview Of New Oral Anticoagulant Toxicity

Kamuran ÇELİK[1], Funda ELUMAR[2]

[1]Uz. Dr. Kamuran ÇELİK Clinic Bursa/Turkey

[2]University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Emergency Medicine Department Bursa/Turkey

Abstract

Atherosclerosis and thrombosis are the underlying causes of stroke and myocardial infarction. Anticoagulants have a significant role in both the prevention and treatment of these conditions. The difficulty of monitoring warfarin derivatives, which have been in use until recently, and their narrow therapeutic range paved the way for the development and use of new oral anticoagulants. Rivaroxaban, Apixaban, Edoxaban, and Betrixaban are Factor Xa inhibitors, while Dabigatran is a Thrombin (FIIa) inhibitor, and together they comprise the new oral anticoagulants. It is crucial to manage any accidental or intentional overdose with these new oral anticoagulants. The present review focuses on the characteristics of novel anticoagulants and their toxicological management.

Introduction

In the 20th and 21st centuries, the improvement in education and income levels and technological advancements contributed to the rise in average life expectancy. However, these developments have also had negative effects on human health. The increase in the means of transportation, the decline in physically demanding jobs, the rise in the workload of desk jobs, and technology dependence have resulted in a more sedentary lifestyle. The deterioration in dietary habits during this period, combined with a lack of physical activity, has contributed to the rise in obesity. Additionally, the increase in tobacco use over the past century played a role in the growing health problems. While all these factors contributed to the rise in the incidence of cardiovascular diseases, acute myocardial infarction and stroke have been among the leading causes of death. Anticoagulants play a vital role in preventing and treating these conditions. Indeed, Warfarin is effective in preventing thromboembolic events. However, its narrow therapeutic range, potential interactions with food and other medications, the need for INR monitoring, and individual variations in treatment response led scientists to explore alternatives that eliminate the need for laboratory monitoring while offering effective treatment with fixed doses.[1]

The Mechanism of Coagulation

Physiological coagulation occurring outside the blood vessels is called haemostasis, while pathological coagulation that occurs within the blood vessels is referred to as thrombosis. If the clot formed during coagulation is attached to the wall of a blood vessel, it is called a thrombus. When it moves freely through the bloodstream, it is called an embolus. Physiological or pathological coagulation occurs as a result of a systemic and complex interaction among platelets, endothelial cells, and coagulation factors. Arterial thrombi can lead to acute myocardial infarction, stroke, and gangrene of the proximal or distal extremities. Venous thrombi, on the other hand, can cause pulmonary embolism and phlebitic syndromes. The coagulation cascade consists of three phases: the platelet phase, the vascular phase, and the plasma phase. In the platelet phase, collagen exposed from the damaged vessel wall binds to the von Willebrand Factor (vWF) present in the plasma. As a result of this

Corresponding Author: Kamuran ÇELİK **e-mail:** drkamurancelik@hotmail.com

Received: 18.12.2024 • **Accepted:** 23.12.2024

Cite this article as: ÇELİK K, ELUMAR F. An Overview Of New Oral Anticoagulant Toxicity. Eurasian J Tox. 2023;6(3): 55-58

bridge formation, platelet adhesion takes place, and platelets are activated. Following adhesion, activated platelets release factors such as adenosine diphosphate (ADP), platelet-derived growth factor (PDGF), and vWF. At this point, ADP promotes the activation of additional platelets while also activating GPIIb/IIIa receptors. Fibrinogen promotes platelet aggregation via these receptors. When endothelial damage occurs, the release of prostaglandin I2 (PGI2, endothelial-derived) decreases, while the release of thromboxane A2 (TxA2, platelet-derived) increases. When endothelial damage is more significant, platelet aggregation and the release of FIII from the damaged endothelium trigger plasma coagulation factors, leading to the formation of FIIa (thrombin). Subsequently, thrombin converts fibrinogen into fibrin, forming a stable clot structure. In this mechanism, thrombin is the strongest platelet activator. There are three groups of drugs used in the treatment of conditions caused by thrombus formation. The first group is antithrombotic agents. This group consists of aspirin, a cyclooxygenase inhibitor; dipyridamole and cilostazol which are phosphodiesterase inhibitors; Clopidogrel, Ticlopidine, Ticagrelor, Cangrelor, and Prasugrel which are inhibitors of ADP receptor; and Abciximab, Eptifibatide, and Tirofiban which are glycoprotein (GP) IIb/IIIa inhibitors. The second group consists of anticoagulant agents. This group includes Warfarin and Dicumarol, which are vitamin K antagonists; Heparin, an inhibitor of thrombin (FIIa) and Factor Xa, as well as thrombin inhibitors, and Factor Xa inhibitors. The third group, namely the fibrinolytic group, includes drugs like Alteplase and Streptokinase, which are plasminogen activators.[2]

New Oral Anticoagulants (NOACs)

Anticoagulants are used in patients with atrial fibrillation (AF) for the prevention of stroke, in the prophylaxis and treatment of deep vein thrombosis (DVT), for the treatment of pulmonary embolism, as well as for secondary prevention of cardiovascular events. Standard heparin, which produces its anticoagulant effect by inhibiting Factor Xa and thrombin, has been in use for the past 50 years. Low molecular weight heparin (LMWH) was introduced for clinical use in the early 1990s. Another oral anticoagulant, the vitamin K antagonist Warfarin, has also been in use. The effectiveness of these drugs (warfarin) has been established, but their narrow therapeutic range, high potential for food and drug interactions, and the need for laboratory monitoring create challenges not only for patients but also for clinicians. As a result of scientific research to develop drugs that would not require monitoring, provide effective treatment with fixed doses, and have a low side effect profile, new oral anticoagulants (NOACs) were developed. Rapid onset of action, oral administration, minimal drug and food interactions, no need for laboratory monitoring, high effectiveness, and low side effect profile are the advantages of using new oral anticoagulants. On the other hand, they have some drawbacks, such as loss of efficacy if doses are missed, limited use in patients with impaired renal function, non-availability of monitoring methods, and absence of established dosing regimens to be followed in the presence of comorbidities. Looking at these two groups of anticoagulants from another perspective, a key difference noted is that the anticoagulants in the warfarin group have a delayed onset of action and require bridge therapy. NOACs are more expensive than the anticoagulants in the warfarin group. New oral anticoagulants include Fondaparinux, which is administered parenterally, Dabigatran, Apixaban, Betrixaban, Edoxaban, and Rivaroxaban, which are taken orally.3 Among these anticoagulants, Betrixaban has the longest duration of action.

Dabigatran

It is a direct thrombin inhibitor, also known as an FIIa inhibitor. It is used for stroke prophylaxis at a dose of 2x150 mg in patients with AF. It is used at a dose of 2x110 mg in patients at high risk of bleeding (a HAS-BLED score of 3 or higher). It is contraindicated in patients with a creatinine clearance of 30 ml/min or lower. Its average half-life is 14 to 17 hours. The most effective test for monitoring toxicity is the Thrombin Time (TT). Approximately 80% of dabigatran is excreted by the kidneys. Dabigatran is the only new oral anticoagulant that can be mostly removed through hemodialysis.4 In the event of Dabigatran toxicity, if the drug was taken within the last 2 to 4 hours, gastric lavage should be performed first, followed by the oral administration of 50 g or 1 g/kg of activated charcoal. Since at least 80% of dabigatran does not bind to serum proteins, hemodialysis should be considered, especially in patients with impaired renal function or in those whose renal function is progressively deteriorating.5 Additionally, idarucizumab, which has an affinity for dabigatran that is 350 times stronger than its affinity for thrombin, has been used in the treatment of dabigatran toxicity.6 Five grams of idarucizumab, administered in two equal doses, completely (100%) reversed the anticoagulant effect of dabigatran within 4 hours. The administration method should involve two equal infusions, each lasting 5 to 10 minutes, with a 15-minute interval between the infusions. The dilute thrombin time and ecarin clotting time (ECT) tests confirmed this result. If idarucizumab is unavailable, prothrombin complex concentrate (PCC) (COFACT) or activated PCC (FEIBA) can be administered at a dose of 50 U/kg, with the maximum being 4000 U. If the active bleeding site can be controlled, pressure or other methods should be used to manage the bleeding. Besides specific treatments, fluid replacement can be also used to maintain hemodynamic stability.

FactorXa Inhibitors

Rivaroxaban, Apixaban, Edoxaban, and Betrixaban are the drugs in this class. Rivaroxaban reaches the peak plasma concentration 3 hours after oral administration. Its half-life is 4 to 9 hours. The drug has minimal food and drug interactions. Its oral bioavailability is over 80%. Two-thirds of the drug is excreted via the liver, and one-third of the drug is eliminated as unchanged drug. The standard dose is 1x20 mg. The dose should be reduced to 1x15 mg in patients with a creatinine clearance of 15 to 49 mg/min. Apixaban does not cause organ toxicity or elevated liver enzymes in liver function tests. It has no food interactions. Its oral bioavailability is above average. Its half-life is approximately 12 hours. Apixaban is used at a dose of 2x5 mg. However, if the patient weighs less than 60 kg, is over 80 years old, or has a serum creatinine level above 1.5, and two of these conditions apply, the dose should be reduced to 2x2.5 mg. The half-life of Edoxaban is 9 to 11 hours. The standard dose of Edoxaban is 1x60 mg. However, if the patient weighs less than 60 kg, has a creatinine clearance of 15 to 49 mL/min, or takes a P glycoprotein inhibitor concurrently, the dose is reduced to 1x30 mg. Betrixaban is the newest oral FXa inhibitor, with the longest half-life, ranging from 19 to 27 hours. It is indicated for long-term thromboembolism prophylaxis, but it is not indicated for stroke prophylaxis in patients with AF.7 Additionally, NOACs are not recommended during pregnancy, in cases of advanced liver failure, severe kidney failure, or dialysis, and for patients with mechanical heart valves, those with moderate to severe mitral valve stenosis, or in individuals with antiphospholipid syndrome. Generally, the plasma levels of NOACs increase when the age of the patient is over 80 years when the patient weighs less than 60 kg, and in cases of renal failure. On the other hand, the efficacy of the anticoagulants may decrease in the obese population due to the reduction in plasma levels. Andexanet alfa has been reported to exhibit a rapid onset of action (within 2 to 5 minutes) by correcting thrombin formation and normalizing coagulation in patients, who were treated with rivaroxaban, apixaban, and edoxaban.8 The drug reduces anti-factor Xa activity by 79% with an initial bolus followed by a 2-hour infusion. Andexanet (recombinant Factor Xa) was approved by the FDA in 2018 and is effective in reversing the effects of FXa inhibitors. Andexanet does not require any dose adjustments for renal failure. It is believed that with the introduction of these antidotes, managing bleeding complications in patients treated with NOACs will become easier.9 In cases of Factor Xa toxicity, another option to be considered is 4F-PCC at a dose of 50 U/kg.10 If it is not available, the third option should be aPCC at a dose of 50 U/kg. If the drug was taken within 2 to 4 hours, gastric lavage followed by the administration of 50 g of activated charcoal should be carried out.11 The anti-Factor Xa chromogenic assay is the preferred method for assessing the anticoagulant activity of apixaban, edoxaban, and rivaroxaban.12

Table 1: Anticoagulants

Mechanism of anticoagulation	Parenteral	Oral
Trombin(FIIa), Fxa inhibitors	Heparin, Danaparoid	
Trombin inhibitors	Hirudin, Bivalurudin, Argatroban	Dabigatran
Fxa inhibitors	Fondaparinux	Rivaroxaban, Apixaban Edoxaban, Betrixaban
Vitamine K antagonist		Warfarine,Dikumarol

Table 2: Treatment of Toxication

Drug	Treatment of Toxication
Dabigatran (Hemodialysis suitable)	Gastric Lavage,Hemodialysis,Actived charcoal,İdaricuzimab(S) *
Apixaban (Hemodialysis non-suitable)	Gastric Lavage,Actived charcoal,Andexanet alfa(S) *, 4F-PCC**
Edoksaban (Hemodialysis non-suitable)	Gastric Lavage,Actived charcoal, Andexanet alfa(S) *, 4F-PCC**
Betrixaban (Hemodialysis non-suitable)	Gastric Lavage,Actived charcoal, Andexanet alfa(S) *, 4F-PCC**
Rivaroksaban (Hemodialysis non-suitable)	Gastric Lavage,Actived charcoal, Andexanet alfa(S) *, 4F-PCC**

*S:Specific, **4F-PCC:Four-Factor prothrombin complex concentrate

General Approach and Conclusion

Bleeding associated with hemodynamic instability, occurring in anatomically critical areas, requiring the transfusion of 2 or more units of red blood cells, or causing a 2 g/dL or higher drop in hemoglobin levels (if baseline values are known) should be considered major bleeding. When we say “critical bleeding areas”, we refer to intracranial hemorrhages (such as subdural, epidural, intraparenchymal, and subarachnoid),

Table 3: Dosage of Antidotes

Drug	Dosage of Antidote
Dabigatran	İdaricuzimab → 2*2,5 gr(5gr)
Apixaban	Andexanet alfa(S) * → 30mg/min totaly 400 mg IV bolus,after 4mg/min 2 hour infusion 4F-PCC** → 50U/kg
Edoksaban	Andexanet alfa(S) * → 30mg/min totaly 400 mg IV bolus,after 4mg/min 2 hour infusion 4F-PCC** → 50U/kg
Betrixaban	Andexanet alfa(S) * → 30mg/min totaly 400 mg IV bolus,after 4mg/min 2 hour infusion 4F-PCC** → 50U/kg
Rivaroksaban	Andexanet alfa(S) * → 30mg/min totaly 400 mg IV bolus,after 4mg/min 2 hour infusion 4F-PCC** → 50U/kg

*S:Specific, **4F-PCC:Four-Factor prothrombin complex concentrate

pericardial tamponade, hemothorax, intra- and retroperitoneal bleeding, bleeding in the respiratory tract, and bleeding in joints. In patients with ongoing bleeding and/or hemodynamic instability, local measures to control bleeding should be combined with fluid resuscitation.13 Intravenous use of isotonic crystalloids such as 0.9% NaCl or Ringer's lactate is recommended for fluid resuscitation. Hypothermia and acidosis should be corrected because these conditions can worsen coagulopathy and contribute to bleeding. In the event of bleeding occurring in the critical anatomical regions, it is crucial to consult the relevant medical unit. In the presence of symptomatic anemia and bleeding, erythrocyte suspension should be administered to maintain the hemoglobin level at 7 g/dL, or 8 g/dL if there is concomitant coronary artery disease. For patients who require three or more units of erythrocyte transfusion within one hour, activation of a massive transfusion protocol should be considered.14 For ES: FFP: PLT, the ≤ 2:1:1 formula is the most frequently applied. In trauma patients, early administration of tranexamic acid within the first 3 hours of admission is associated with reduced bleeding and lower mortality and should be considered for use.15 Tranexamic acid should be initiated with a bolus dose of 10 to 20 mg/kg, followed by repeated doses of 10 mg/kg every 8 hours. In individuals with liver disease, INR, PT, and aPTT may not be reliable indicators for assessing hemostatic function. For this reason, further evaluation and hematology consultation should be considered in case of doubt. When necessary and if available, cryoprecipitate transfusion can be administered to maintain fibrinogen levels >100 mg/dL. Reversing the effect of NOACs is not recommended unless there is major bleeding.

References

1. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood, 2010;115(1), 15–20. https://doi.org/10.1182/blood-2009-09-241851
2. Atalan N. Hemostaz. GKD Anest Yoğ Bak Dern Derg, 2013;19(3), 109-112. https://doi.org/10.5222/GKDAD.2013.109.
3. Acar BA, Akpınar ÇK, Alioğlu Z, Arlıer Z, Arsava EM, Aytaç E, et al. İnme klinik pratiğinde NOAK kullanımı: Türk Beyin Damar Hastalıkları Derneği Uzman Görüşü. Türk Beyin Damar Hastalıkları Dergisi 2020;26(3):190-235. https://doi.org/10.5505/tbdhd.2020.26213
4. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clinical pharmacokinetics, 2008;47(5), 285–295. https://doi.org/10.2165/00003088-200847050-00001
5. McBride L, Wang J, Ho P, Langsford D. Dabigatran Toxicity in Acute Kidney Injury: Hemodialysis and Idarucizumab Required. Kidney international reports, 2008;4(3), 500–504. https://doi.org/10.1016/j.ekir.2018.11.015
6. Pollack CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. The New England journal of medicine, 2017;377(5), 431–441. https://doi.org/10.1056/NEJMoa1707278
7. Miller KM, Brenner MJ. Betrixaban for Extended Venous Thromboembolism Prophylaxis in High-Risk Hospitalized Patients: Putting the APEX Results into Practice. Drugs, 2019;79(3), 291–302. https://doi.org/10.1007/s40265-019-1059-y
8. Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Członkowska A, Lindgren AG, et al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. The New England journal of medicine, 2024;390(19), 1745–1755. https://doi.org/10.1056/NEJMoa2313040
9. Milling TJ, Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, et al. Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. Circulation, 2023;147(13),1026–1038. https://doi.org/10.1161/CIRCULATIONAHA.121.057844
10. Dobesh PP, Fermann GJ, Christoph MJ, Koch B, Lesén E, Chen H, et al. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. Research and practice in thrombosis and haemostasis, 2023;7(6), 102192. https://doi.org/10.1016/j.rpth.2023.102192
11. Neumann MA, Sieg N, Garcia Borrega J, Hüser C, Caspers M, Shimabukuro-Vornhagen A, et al. Überdosierung von direkten oralen Antikoagulanzien [Overdosing of direct oral anticoagulants]. Medizinische Klinik, Intensivmedizin und Notfallmedizin, 2024;10.1007/s00063-024-01154-8. Advance online publication. https://doi.org/10.1007/s00063-024-01154-8
12. Boissier E, Senage T, Babuty A, Gouin-Thibault I, Rozec B, Roussel JC, et al. Heparin Anti-Xa Activity, a Readily Available Unique Test to Quantify Apixaban, Rivaroxaban, Fondaparinux, and Danaparoid Levels. Anesthesia and analgesia, 2021;132(3), 707–716. https://doi.org/10.1213/ANE.0000000000005114
13. Bonanno FG. Management of Hemorrhagic Shock: Physiology Approach, Timing and Strategies. Journal of clinical medicine, 2022;12(1),260. https://doi.org/10.3390/jcm12010260
14. Galvagno SM, Nahmias JT, Young DA. Advanced Trauma Life Support Update 2019: Management and Applications for Adults and Special Populations. Anesthesiology clinics, 2019;37(1),13–32. https://doi.org/10.1016/j.anclin.2018.09.009
15. Trauma and severe bleeding. Tranexamic acid within one hour to reduce mortality. Prescrire international, 2013;22(140), 189–190.