Novel Anticoagulant Agents in the Perioperative Setting

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KEYWORDS

• Anticoagulation • Novel oral anticoagulants • Regional anesthesia
• Neuraxial anesthesia • Perioperative management • ASRA guidelines

KEY POINTS

- An increasing number of oral anticoagulants have become available over the past decade. Each of these agents has differing implications on both regional and neuraxial anesthetic techniques.
- This article describes the pharmacology, pharmacokinetics, and pharmacodynamics of novel oral anticoagulants.
- It also describes the preoperative management of the novel oral anticoagulants and their implications for general and regional anesthesia.

INTRODUCTION

Novel oral anticoagulants (NOACs) have increased in popularity and use over the past 10 years (**Table 1**). They are approved for use for prevention of stroke in nonvalvular atrial fibrillation, deep vein thrombosis (DVT)/pulmonary embolism (PE) treatment, and prophylaxis for DVT for some surgical procedures. NOACs were introduced as a replacement for warfarin because they are the first oral anticoagulants that do not require frequent laboratory monitoring. On the downside, compared with warfarin, there are no specific reversal agents for bleeding and there is also a lack of randomized controlled trials showing safety in the timing of surgical procedures and regional anesthetic techniques. At present, guidelines are based mostly on drug half-life and other limited data. As a result, there continue to be differing opinions about discontinuation of NOACs in the published literature. In this comprehensive review we describe

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Table 1
Novel oral anticoagulants

Direct Thrombin Inhibitor	Factor Xa Inhibitors	Antiplatelet Agents (P2Y12 Receptor Antagonists)
• Dabigatran	• Rivaroxaban • Apixaban • Edoxaban • Betrixaban	• Clopidogrel • Prasugrel • Ticagrelor

the pharmacology and pharmacokinetics of the NOACs and discuss implications for perioperative care.

DIRECT THROMBIN INHIBITORS

Dabigatran Etexilate

Dabigatran etexilate is currently the only oral direct thrombin inhibitor on the market. It has been approved for prevention of stroke in nonvalvular atrial fibrillation, treatment of acute venous thromboembolism (VTE), and prevention of VTE after total joint surgery. Dabigatran etexilate is an oral prodrug that is rapidly absorbed in the stomach, with peak plasma concentrations reached within 2 hours,[1] and then converted to its active form, dabigatran. Its bioavailability is estimated at about 7%.[2] It reversibly binds to thrombin to inhibit its activity in the coagulation cascade and prevent the formation of fibrin from fibrinogen and also prevents activation of factors V, VIII, and X. Following absorption, dabigatran undergoes rapid redistribution and has an elimination half-life of 12 to 17 hours in healthy adults.[1] In patients with end-stage renal disease, the half-life is prolonged to approximately 28 hours.[3] Therefore, the dose should be adjusted for renal function and if creatinine clearance is estimated to be less than 30 mL/min, dabigatran use is contraindicated.[4] It does not undergo metabolism by the cytochrome P (CYP) 450 system and undergoes 80% renal excretion and 20% gastrointestinal (GI) excretion.[5] Moderate hepatic impairment has not been shown to affect the pharmacokinetics of dabigatran and therefore these patients do not require a dose adjustment.[6]

At present the only reversal techniques available for dabigatran include hemodialysis and activated charcoal administered within 1 to 2 hours of oral dosing. Idarucizumab, an antibody fragment that is specific in the reversal of dabigatran, is currently undergoing testing and clinical trials. Small studies have shown complete reversal of dabigatran within minutes of administration of idarucizumab and it is currently undergoing clinical trials.[7]

FACTOR XA INHIBITORS

There are currently 4 available orally active factor Xa inhibitors on the market with more in development. Direct factor Xa inhibitors work by binding to free factor Xa and factor Xa bound to the prothrombinase complex and therefore interrupt both the intrinsic and extrinsic coagulation cascade, preventing the ultimate formation of thrombin.

Rivaroxaban

Rivaroxaban was the first available orally active factor Xa inhibitor. In the United States, it is currently approved for use in prevention of VTE and stroke in patients with nonvalvular atrial fibrillation, treatment of VTE, and for the prevention of VTE after orthopedic surgery. It has also been shown to have benefit in patients with recent