Update on Direct Oral Anticoagulants and Their Uses

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KEYWORDS

• Direct oral anticoagulants • Warfarin • Atrial fibrillation • Venous thromboembolism

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Anticoagulants are beneficial for treatment of venous thromboembolism and prevention of stroke in atrial fibrillation.
2. Direct oral anticoagulants (DOACs) are a growing alternative to warfarin because of their predictable pharmacokinetics and ease of use.
3. There is an advent of rapid and safe reversal agents for DOACs for use in situations of major bleeding and preprocedurally.

INTRODUCTION

Direct oral anticoagulants (DOACs) are rapidly gaining traction as the preferred method of oral anticoagulation for patients with nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), and for prophylaxis of deep vein thrombosis (DVT). Their predictable pharmacokinetic properties allow easy dosing regimens that avoid many of the difficulties and challenges associated with vitamin K antagonist (VKA) therapy. However, the DOAC agents pose unique challenges for health care providers, who have previously developed comfortable strategies to manage VKAs and must now adapt to a new class of medications. This article reviews the indications

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and dosing considerations, clinical efficacy and safety, laboratory monitoring, and reversibility considerations of DOACs.

DOACs include oral direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors such as dabigatran.

MECHANISM OF ACTION AND PHARMACOLOGY

Direct Thrombin Inhibitors

Dabigatran etexilate, a prodrug of dabigatran, is the only commercially available oral direct thrombin inhibitor, or inhibitor of factor IIa. Dabigatran is a small, synthetic molecule that specifically and reversibly inhibits free and clot-bound thrombin by binding to the active site of thrombin.[1] Inhibition of thrombin attenuates formation of fibrin, reduces thrombin generation, and may limit platelet aggregation.

Oral Activated Factor X Inhibitors

Factor Xa inhibitors bind directly to the active site of factor Xa, located at the convergence of the intrinsic and extrinsic pathways in the coagulation cascade. Inhibition at this site blocks thrombin generation from both pathways, and prevents subsequent amplification of thrombin generation, and thrombin-mediated activation of coagulation and platelets.[2]

The DOAC plasma concentration reaches their peak at 1 to 4 hours. Therefore, the therapeutic effect of DOACs occurs more rapidly and the risk of bleeding increases proportionately. The bioavailability of most of the DOACs is between 60% and 100%. The exception is dabigatran, which has low bioavailability, therefore requiring a higher dosage. The high bioavailability of DOACs contributes to a more predictable anticoagulant response, eliminating the need for routine monitoring.

The metabolism of DOACs is mainly performed by the liver. There may be interpatient variability when these drugs are given to patients with moderate hepatic disease,[3] and they must therefore be used with caution in such patients. Most of the DOACs are excreted renally, with primary excretion rates ranging from 60% to 85%, except for apixaban and edoxaban, which have a much lower excretion rates. Therefore, patients with impaired renal function can have increased plasma drug concentrations.

LABORATORY MONITORING OF DIRECT ORAL ANTICOAGULANTS

With the use of VKA for anticoagulation, clinicians have become accustomed to checking International Normalized Ratio (INR) values to assess how well patients are being anticoagulated and adjust VKA dosing. The DOACs challenge this paradigm by offering predictable pharmacokinetics, thus eliminating the need for routine laboratory monitoring. However, there are certain clinical scenarios when laboratory monitoring is clinically warranted, such as before urgent or emergent surgery, when assessing medication compliance, and for ensuring adequate anticoagulation in patients at the extremes of weight. A few routine laboratory tests are available that, when properly calibrated, can offer insight into the degree of anticoagulation for patients taking DOACs. For patients taking dabigatran, a normal thrombin time can be used to rule out any clinically relevant anticoagulation.[4] The dilute thrombin time is the best option for assessing whether patients are appropriately or overly anticoagulated, but this test is not universally available. A normal activated partial thromboplastin time likely excludes supratherapeutic levels of dabigatran.

For patients taking rivaroxaban, apixaban, or edoxaban, use of the anti-Xa activity can reliably assess the degree of anticoagulation across a wide range of drug concentrations, including subtherapeutic, therapeutic, and supratherapeutic levels.[5] This