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Review

New-generation oral anticoagulants for the prevention of stroke: Implications for neurosurgery

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ABSTRACT

A new generation of oral anticoagulants, namely direct thrombin inhibitors and factor X_a inhibitors, have recently been approved for clinical use in patients with atrial fibrillation. These novel families of drugs have been shown to have favorable efficacy and safety profiles in multiple clinical settings, particularly in the prevention of atrial fibrillation-related stroke, and are likely to become part of everyday practice, making a crossover to neurosurgical patients inevitable. Concern has risen regarding the complexity of managing intracranial and intraspinal hemorrhages related to these drugs. This review aims to provide an update on the most recent advances in oral anticoagulant drug therapy from a neurosurgeon's perspective. We discuss current evidence for the use of these novel agents, their limitations, existing methods of drug-level monitoring, and controversies related to anticoagulation reversal. We also discuss specific topics such as anticoagulation resumption after intracranial or intraspinal bleeding, perioperative anticoagulant administration, and the possibility of combination with tissue plasminogen activator in the setting of acute ischemic stroke. A special focus is given to the incidence of intracranial and intraspinal hemorrhage associated with each drug.

1. Introduction

The age-adjusted stroke death rate in the USA has steadily declined since 1931.[1] This decrease is due primarily to the steady effort to optimize cerebrovascular risk factor control, the increase in the use of anticoagulants, and the implementation of advanced, life-saving procedures in acute stroke management. Atrial fibrillation (AF) is an important risk factor prevalent among 23.5% of elderly patients affected by stroke.[2] Ischemic cerebral infarcts complicating AF tend to be large and cause significant morbidity.[3] For more than 60 years, the vitamin K antagonist warfarin has been the primary long-term oral anticoagulant proven to significantly reduce AF-related thromboembolic events.[4] This drug, however, has multiple limitations and side effects. Most importantly, warfarin increases the risk of major bleeding, with intracranial hemorrhage responsible for the highest percentage of drug-induced morbidity and mortality.[5]

Recently, a new generation of oral anticoagulants, known as direct thrombin inhibitors (DTI) and factor X_a inhibitors (FX_aI), have been approved for clinical use in patients with AF. These novel pharmaceuticals have demonstrated efficacy and safety profiles comparable to warfarin in multiple clinical settings.[6–8] Because of their prospective benefits, the new anticoagulants will likely be integrated into everyday practice. However, concern exists regarding the complexity of managing intracranial and intraspinal hemorrhages related to these drugs.[9]

2. Thrombin and oral DTI

Thrombin, or factor II_a, is the final product of a series of proenzyme activation processes known as the "coagulation cascade" (Fig. 1).[10] Thrombin cleaves fibrinogen to fibrin and activates factor XIII, leading to the formation and stabilization of the blood clot.[11] Accordingly, direct and selective targeting of thrombin has been a subject of investigation. Dabigatran etexilate mesylate (BIBR 1048 and Pradaxa, both Boehringer Ingelheim, Ingelheim am Rhein, Germany)[12] (Table 1) is an oral DTI that has been approved by the USA Food and Drug Administration (FDA) in 2010 for the prevention of stroke and systemic embolism in patients with non-valvular AF.[13] Three major randomized clinical trials have assessed the efficacy and safety of dabigatran in this clinical setting. (Table 2).[5,14,15]

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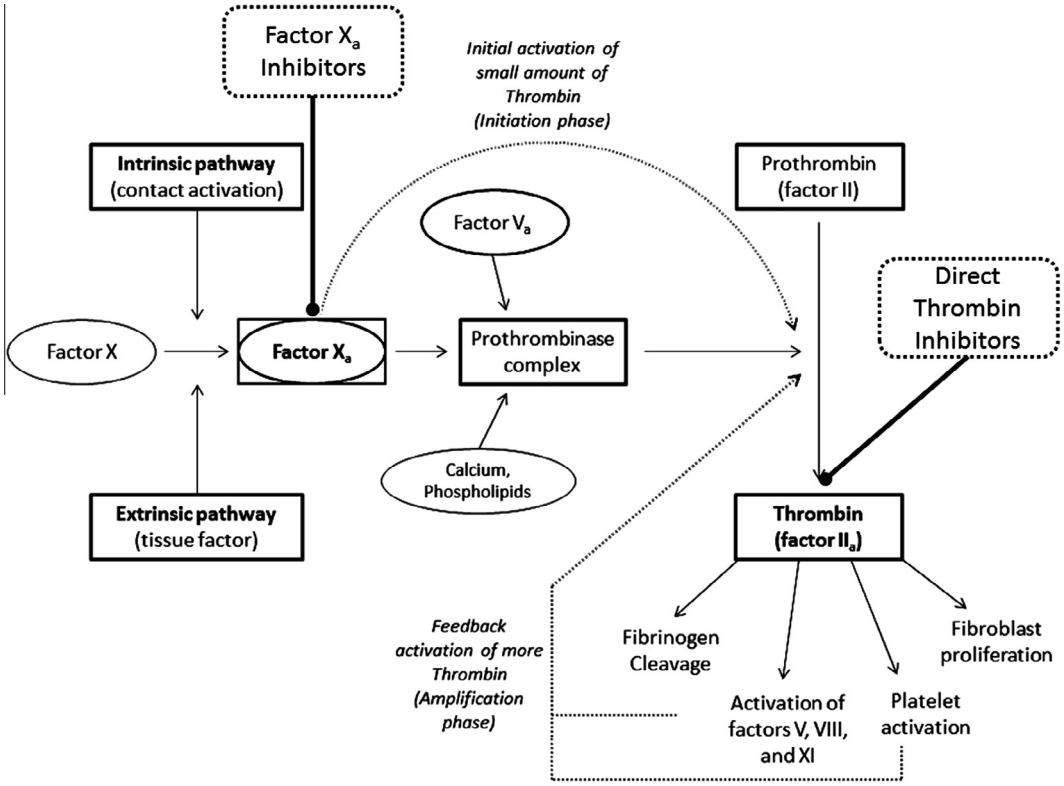

Fig. 1. Diagram showing the mechanism of action of direct factor X_a and thrombin inhibitors.

3. Factor X and oral direct FX_aI

Factor X is an important component of the coagulation cascade located upstream to thrombin (Fig. 1). The activation of factor X into factor X_a is the first step in the common pathway of thrombin formation.[16] As a result, factor X_a has been an appealing target for novel anticoagulation agents. Two major FX_aI are currently used in clinical practice; (1) rivaroxaban (molecular name: BAY 59-7939 [Bayer HealthCare, Leverkusen, Germany]; commercially available as: Xarelto [Johnson & Johnson, Piscataway, NJ, USA])[17] and (2) apixaban (molecular name: BMS-562247-01 [Bristol-Myers Squibb, New York, NY, USA]; commercially available as: Eliquis [Pfizer, New York, NY, USA]).[18] Other FX_aI that are still under investigation include edoxaban (molecular name: DU-176b [Daiichi Sankyo, Tokyo, Japan])[19] and betrixaban (molecular name: PRT-054021 [Portola Pharmaceuticals, San Francisco, CA, USA/Merck, Whitehouse Station, NJ, USA])[20] (Table 1).

Rivaroxaban is an oral FX_aI that was approved by the FDA in 2011 for the prevention of non-valvular AF-related stroke and systemic embolism.[21] More recently, apixaban has received FDA approval for the same indication.[22] Edoxaban is currently under clinical investigation in an ongoing phase III, randomized controlled clinical trial (ENGAGE AF-TIMI 48).[23] Betrixaban is another FX_aI currently under study in the phase II clinical trial EXPLORE-X_a.[24,25] The clinical trials of these four drugs are summarized in Table 3.[7,8,23–26]

4. Discussion

Despite over 60 years of clinical experience, warfarin remains a challenging and sometimes distressing drug, particularly in the emergency setting of ischemic or hemorrhagic stroke and the perioperative setting. It is now likely that novel oral anticoagulants will be increasingly prescribed by internists and general practitioners, at least for patients who are not eligible for warfarin administration. Additionally, patients are likely to start asking about these alternative drugs, which are marketed as easier to use, more efficient, and safer than warfarin. It has thus become crucial for all physicians, especially neurosurgeons, to become aware of the nuances of these novel anticoagulants, recognize their current limitations, and help construct rational algorithms for the management of their complications.

4.1. Anticoagulant-associated intracerebral hemorrhage

Anticoagulant-associated intracerebral hemorrhages (ICH) have larger initial hematoma volumes (especially with international normalized ratio values >3.0)[27] and longer durations of hematoma expansion compared to spontaneous ICH.[28] Accordingly, they carry a worse prognosis, with a mortality rate greater than 50%.[29] DTI and FX_aI share the unique and valuable capacity to preserve cerebral hemostasis.[5,8] The RE-LY[5] trial showed that the 150 mg and 110 mg twice-daily doses of dabigatran reduced the risk of ICH by 60% and 69% compared to warfarin, respectively (Table 4). Moreover, in the ROCKET-AF [8] and ARISTOTLE[7] trials, the 20 mg daily dose of rivaroxaban and 5 mg twice-daily dose of apixaban reduced the risk of ICH relative to warfarin by 33% and 58%, respectively (Table 4). Of note, although the overall risk of major bleeding was not significantly reduced by the 20 mg daily rivaroxaban dose and the 150 mg dabigatran dose compared to warfarin, the likelihood of ICH was significantly reduced. These findings suggest that novel oral anticoagulants could have the advantage of less intracranial adverse events compared to warfarin, regardless of major bleeding rates.

Current hypotheses suggest that novel oral anticoagulants, in contrast to warfarin, can maintain hemostasis in critical areas by selectively targeting a single factor in the coagulation cascade (thrombin or factor X_a). Factor VII_a is preserved when using these agents and is able to bind freely to the tissue factor present in high