Warfarin and Newer Agents
What the Oral Surgeon Needs to Know

Martin B. Steed, DDS*, Matthew T. Swanson, DDS

KEYWORDS

• Dabigatran • Rivaroxaban • Apixaban • Warfarin • Praxbind • Factor Xa inhibitors • Andexanet alfa

KEY POINTS

- Thromboprophylaxis with anticoagulants is an important aspect of managing patients at risk of systemic or pulmonary embolization.
- Dabigatran is a direct inhibitor of thrombin (Factor IIa).
- Rivaroxaban and apixaban inhibit Factor Xa.
- Monitoring of coagulation function is not routinely necessary with these new drugs but may be useful in emergencies.
- Praxbind in the only reversal agent approved by the US Food and Drug Administration for specific emergency situations.
- Nonspecific hemostatic agents that have been suggested for off-label use in reversing excessive bleeding in patients taking the new oral anticoagulants include recombinant Factor VIIa, 3-factor and 4-factor prothrombin complex concentrate, and activated prothrombin complex concentrate.

INTRODUCTION

The management of perioperative bleeding is a fundamental skill of the oral and maxillofacial surgeon that requires continual re-education as new medications become available for anticoagulation. In addition to vitamin K antagonists and heparins, anticoagulants that directly target the enzymatic activity of thrombin and Factor Xa have been developed. These are termed direct oral anticoagulants (DOACs).[1] Familiarity with the pharmacology of newer agents is essential for preoperative and postoperative management in order to safely treat anticoagulated patients.

The management of anticoagulation in patients undergoing surgical procedures is challenging, because interrupting anticoagulation for a procedure transiently increases the risk of thromboembolism. At the same time, surgery and invasive procedures have associated bleeding risks that are increased by the anticoagulants administered for venous thromboembolism prevention. If significant bleeding can be anticipated from the procedure (ie: free fibular osseomyocutaneous flap or coronal incision), their anticoagulant may need to be discontinued for a longer period, resulting in a longer period of increased thromboembolic risk. A personalized balance between reducing the risk of thromboembolism and preventing excessive bleeding must be reached for each patient.

Additional issues relate to the specific anticoagulant used. All anticoagulants increase bleeding risk. For those taking a vitamin K antagonist (eg, warfarin), it takes several days until the anticoagulant effect is reduced and then re-established

Disclosure Statement: The authors have nothing to disclose.
Department of Oral and Maxillofacial Surgery, Medical University of South Carolina, Room BSB 453 MSC 507, 173 Ashley Avenue, Charleston, SC 29425, USA
* Corresponding author.
E-mail address: steedma@musc.edu

Oral Maxillofacial Surg Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.coms.2016.06.011

perioperatively. The risks and benefits of bridging with a shorter-acting agent, such as heparin, during this time remain unclear. The newer direct oral anticoagulants (ie: direct thrombin inhibitor dabigatran, Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban) have shorter half-lives, making them easier to discontinue and resume rapidly, but they lack a specific antidote or reversal strategy.[2] This raises concerns about treatment of bleeding and management of patients who require an urgent procedure as in the maxillofacial trauma patient. Interruption of anticoagulation temporarily increases thromboembolic risk, and continuing anticoagulation increases the risk of bleeding associated with invasive procedures; both of these outcomes adversely affect mortality. The approach to perioperative management of anticoagulation takes into account these risks, along with specific features of the anticoagulant the patient is taking.

Of note, many current approaches are based only at the evidential level of expert opinion.[3,4] Thrombotic and bleeding risks may vary depending on individual circumstances, and data from randomized trials are not available to guide practice in many settings. In addition, the best surrogate for complete resolution of anticoagulant effect is not always known or available for the newer target-specific anticoagulants. Thus, this approach should be used as a guideline and should not substitute for clinician judgment in decisions about perioperative anticoagulant management.

An approach to decision making is outlined in this article.

ESTIMATE THROMBOEMBOLIC RISK

A higher thromboembolic risk increases the importance of minimizing the interval without anticoagulation. Thromboembolic risk for patients with atrial fibrillation is estimated based on age and comorbidities. For those with a recent deep vein thrombosis or pulmonary embolism, the risk is estimated based on the interval since diagnosis. If thromboembolic risk is transiently increased (ie, recent stroke or pulmonary embolism), surgeons should delay surgery until the risk returns to baseline, if possible. For patients with more than 1 condition that predisposes to thromboembolism, the condition with the highest thromboembolic risk takes precedence.

ESTIMATE BLEEDING RISK

A higher bleeding risk confers a greater need for perioperative hemostasis, and hence a longer period of anticoagulant interruption. Bleeding risk is dominated by the type and urgency of surgery; some patient comorbidities also contribute. Procedures with a low bleeding risk (ie: dental extractions or minor skin surgery) often can be performed without interruption of anticoagulation.

DETERMINE THE TIMING OF ANTICOAGULANT INTERRUPTION

The timing of anticoagulant interruption depends on the specific agent the patient is receiving. For example, warfarin requires earlier discontinuation than the shorter-acting target-specific oral anticoagulants (ie: dabigatran, rivaroxaban, apixaban) (Table 1).

DETERMINE WHETHER TO USE BRIDGING ANTICOAGULATION

For patients receiving warfarin, the interval without an anticoagulant may be as long as 5 to 6 days due to the long half-life of warfarin and time to reach the therapeutic international normalized ratio (INR) range. The use of heparin or low molecular weight heparin (LMWH) to reduce the interval without anticoagulation (ie, bridging anticoagulation) may be appropriate for some patients, especially those who have a high thromboembolic risk.

DIRECT ORAL ANTICOAGULANTS

Xa Inhibitors

Direct Factor Xa inhibitors are a new class of anticoagulation medications that are increasingly being substituted for vitamin K antagonists and LMWH for appropriate patients (Fig. 1). The xabans (Xa ban = inhibitor) include rivaroxaban, apixaban, edoxaban, and Betrixaban (in development) act directly on Factor Xa in the coagulation cascade and are gaining popularity due to the need for less monitoring, fairly quick onset and offset of action, few drug interactions, and no food interactions, which provide a greater convenience to patients and a more consistent therapeutic blood level.

IIa Inhibitors

Direct thrombin inhibitors, dabigatran, bivalirudin, argatroban, desirudin, are similar to the Xa inhibitors, but target Factor IIa and cause direct inhibition of thrombin. These too have few drug interactions and no food interactions, making them a popular alternative to warfarin.

MECHANISM OF ACTION

Direct Factor Xa inhibitors work by preventing Factor Xa from cleaving prothrombin to thrombin.