REVIEW ARTICLE

Management of patients taking rivaroxaban for dental treatments

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ABSTRACT

There are several novel anticoagulant drugs that are being increasingly used as an alternative to warfarin and acenocoumarol. Novel oral anticoagulants have emerged in recent years to overcome some of the drawbacks of classic oral anticoagulants. Rivaroxaban, dabigatran, apixaban, and edoxaban were approved by the Food and Drug Administration and European Medicines Agency. This paper examines the available evidence regarding rivaroxaban and sets out proposals for the clinical guidance of dental practitioners treating these patients in primary dental care. Literature search was conducted through May 2016 for publications in the ISI Web of Knowledge, PubMed, and Cochrane Library using the keywords, "rivaroxaban," "dabigatran," "apixaban," "edoxaban," "new oral anticoagulants," "novel oral anticoagulants," "bleeding," and "dental treatment." For patients requiring minor oral surgery procedures, interruption of rivaroxaban is not generally necessary while a higher control of bleeding and discontinuation of the drug (at least 24 h) should be requested before invasive surgical procedure, depending on renal functionality. Their increased use means that oral care clinicians should have a sound understanding of the mechanism of action, pharmacology, reversal strategies, and management of bleeding in patients taking rivaroxaban. Currently, recommendations are based on poor quality scientific data and clinical trials are required to establish best evidence-based practice guidance.

Key words
Apixaban, bleeding, dabigatran, edoxaban, novel oral anticoagulants, rivaroxaban

INTRODUCTION

Patients taking oral anticoagulants or antiplatelet drugs for prevention in nonvalvular atrial fibrillation frequently require dental treatment. The number of anticoagulated patients in developed countries is high, and for decades, this preventive treatment has been based on the administration of warfarin or acenocoumarol. The management of Vitamin K-dependent oral anticoagulants is complex; they require regular international normalized ratio monitoring, have a narrow therapeutic window, and have potential drug–drug and drug-food interactions.

Four new oral anticoagulants (NOACs) have been developed since 2012, all of them approved by the Food and Drug Administration and by the European Medicines Agency (EMA). The first was dabigatran (Pradaxa®), followed by rivaroxaban (Xarelto®), apixaban (Eliquis®), and the latest, edoxaban (Lixiana®). Rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor.[1,2]

Rivaroxaban is a powerful factor Xa inhibitor. By binding to the active site of factor Xa, it inhibits it in a reversible and competitive way. Peak plasma levels are reached 3 h following administration. Its protein binding is >90%, its bioavailability is >80%, and it is not dialyzable. Its half-life is between 5 and 9 h. Approximately 33% is excreted unchanged in urine; 33% is metabolized to inactive metabolites by the kidneys and 33% by the liver.[3]

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One of the disadvantages of NOACs, rivaroxaban included, was the lack of an effective antidote. The results of the ANNEXA-R study with andexanet alfa were presented in 2014, showing that this substance has properties for reversing the effects of NOACs including rivaroxaban. The development of these new substances contributes toward the disappearance of one of the shortcomings of NOACs: The lack of an antidote to reverse their effect. The marketing authorization for this drug is yet to be obtained.[4]

The Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) clinical trial evaluated rivaroxaban versus warfarin in 14,264 patients with nonvalvular atrial fibrillation. The results of the study proved that rivaroxaban was noninferior to warfarin.[5]

The EMA authorized the marketing of rivaroxaban for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation. The usual dose of rivaroxaban for these cases is 20 mg every 24 h, which should be lowered to 15 mg every 24 h in patients with moderate renal impairment (creatinine clearance 15–50 ml/min).[6]

MATERIALS AND METHODS

The aim of this paper is to contribute toward the discussion on how to approach patients taking rivaroxaban, before, during, and after dental treatments.

In the present contribution, we offer an exhaustive review of the literature found in the ISI Web of Knowledge, PubMed, and Cochrane Library in May 2016. The words used were “rivaroxaban,” “dabigatran,” “apixaban,” “edoxaban,” “new oral anticoagulants,” “novel oral anticoagulants,” “bleeding,” and “dental treatment” with the “and” Boolean operator.

Because of their relatively recent introduction, specific studies regarding dental treatment of patients taking novel oral anticoagulants are available in literature only from 2012.

Drug interactions

Classic Vitamin K-dependent oral anticoagulants present many drug–drug and drug-food interactions that may result in potentiation, increasing the risk of bleeding or decreasing their effectiveness. There is currently scarce evidence of the interaction of NOACs with other drugs or certain foods.

Rivaroxaban is a substrate of P-glycoprotein, a transporter that hinders the absorption of certain substances. P-glycoprotein activators lower rivaroxaban plasma concentrations, whereas P-glycoprotein inhibitors increase absorption.

Phenytoin, rifampicin, and carbamazepine reduce the effect of rivaroxaban. Use with other anticoagulants, azole antifungals (such as itraconazole and ketoconazole), or HIV-protease inhibitors (such as ritonavir) is not recommended since all these drugs potentiate the effect of rivaroxaban. Caution is advised when rivaroxaban is combined with erythromycin or clarithromycin.[7,8]

Rivaroxaban plasma levels fundamentally depend on dosage, with little variation among individuals. Taking the standard administration guidelines of 20 mg every 24 h, peak plasma concentrations can reach 200 pg/L of plasma; this peak plasma concentration increases in patients with moderate renal impairment and elderly patients.

Analytical tests

Regular hemostatic tests show low sensitivity to rivaroxaban. There are specific coagulation tests to determine plasma rivaroxaban levels although they are scarcely used and costly techniques.[9]

Prothrombin time: The increase in prothrombin time is proportional to plasma rivaroxaban concentrations. Normal prothrombin time is considered to exclude the presence of rivaroxaban in the blood. This is considered to be the most useful of the existing coagulation tests. A disadvantage is that when plasma rivaroxaban levels are below 200 pg/L, the linear increase of rivaroxaban does not go beyond 1.5 times the control value.[10,11]

Activated partial thromboplastin time: Activated partial thromboplastin time becomes increased only when plasma rivaroxaban concentrations reach peak values, which is approximately 4 h after its administration. When rivaroxaban concentrations are below 200 pg/L of plasma, the activated partial thromboplastin time is practically unnoticeable.[12,13]

Chromogenic assays to quantify the activity of rivaroxaban: The main disadvantage is their high cost. These tests make it possible to assess the anti-Xa activity of rivaroxaban.[14,15]

Perioperative management

As with other anticoagulant and antiplatelet drugs, patients taking rivaroxaban are at higher risk of bleeding when undergoing invasive dental procedures.[16]

According to the ROCKET-AF trial, the rate of low bleeding complications was 4%–7%, while the rate of severe bleeding complications was 2.3%. These rates were similar in patients in the warfarin and the rivaroxaban groups.[17]

There are certain situations that require temporary discontinuation of rivaroxaban before the dental procedure. When to temporarily discontinue rivaroxaban depends on the bleeding risk involved in the dental procedure to be performed. Based on the bleeding risk involved, dental treatments can be classified into low-risk procedures and average- or high-risk procedures.[18]

Dental procedures with low bleeding risk: These cases do not require discontinuation of rivaroxaban. The dental treatment should be conducted 20 h from the administration of the drug. This group includes simple extractions, oral surgery of up to 45 min, and periodontal surgery with minimal bleeding risk.[19-21]

Dental procedures with average and high bleeding risk: These cases require temporary discontinuation of rivaroxaban. When to discontinue rivaroxaban depends on the patient's renal function and the drug's plasma half-life [Table 1].[22-24]

Postoperative management

When to resume rivaroxaban after the dental procedure depends on the patient's hemostasis and the bleeding risk involved in the dental treatment.

Patients with low bleeding risk can restart treatment with their usual dose of rivaroxaban after 12 h.

The treatment of bleeding after dental procedures should be individualized according to the severity of the bleeding.

In cases of mild bleeding, it is enough to use local hemostatic measures such as sutures, gelatin or cellulose sponges, and tranexamic acid mouthwashes, which help to reduce the chance of postoperative bleeding.[25,26]

In moderate and severe bleeding, the patient should be referred to a hospital. Among the measures to treat moderate and severe bleeding are the maintenance of an adequate diuresis to enhance the elimination of the drug, the transfusion of platelet concentrates, and the administration of nonactivated prothrombin complex concentrates.[27,28]

CONCLUSIONS

In dentistry and oral surgery, the major concern in the treatment of patients taking oral anticoagulants or antiplatelet drugs is the risk of hemorrhage.

Table 1: Rivaroxaban discontinuation guidelines

	Standard bleeding risk (h)	High bleeding risk (h)
CrCl >30 (ml/min)	24	48
CrCl <30 (ml/min)	48	96

CrCl – Creatinine clearance

There are several novel oral anticoagulant agents that are being increasingly used as an alternative to warfarin and acenocoumarol.

There is little published in the current literature specific to professionals involved in oral health care.

For patients requiring simple dental extraction or minor oral surgery procedures, interruption of rivaroxaban is not generally necessary while a higher control of bleeding and discontinuation of the drug (at least 24 h) should be requested before invasive surgical procedures.

The clinician has to consider that the number of patients taking novel oral anticoagulants (rivaroxaban, dabigatran, apixaban, and edoxaban) is rapidly increasing. Since available data are not sufficient to establish an evidence-based dental management, the dentist must use caution and attention when treating patients taking rivaroxaban.

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Conflicts of interest

There are no conflicts of interest.

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