Review Article

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New Generation Direct Oral Anticoagulants and their Dental Implications

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ABSTRACT

Background: Patients taking antithrombotic medications frequently require dental treatment. Four novel direct oral anticoagulants (DOACs) named Dabigatran, Rivaroxaban, Edoxaban and Apixaban have been recently introduced to overcome some of the drawbacks of existing antithrombotic. Compared with warfarin, the next generation of orally administered anticoagulants ideally has a wide therapeutic index, less complex pharmacodynamics, few drug-drug and food interactions. Dentists are aware of periprocedural management of traditional antithrombotic medications; there is a significant lack of knowledge about the new agents. This article describes the dental implications of these new oral anticoagulants, and there potential interactions with drugs prescribed in routine dental treatments.

Keywords: Anticoagulant, Direct oral anticoagulants (DOAC), Dabigatran, Rivaroxaban.

INTRODUCTION

With the turn of the century cardiovascular diseases have now become the leading cause of mortality in India [1]. With the increase in number of cardiovascular diseases the need for newer DOACs arises. Oral anticoagulants and antiplatelet drugs are used for primary and secondary prevention of venous thromboembolic diseases. Vitamin K antagonist anticoagulant drugs have been widely used for the treatment of nonvalvular atrial fibrillation. For decades, dicoumarin derivative oral anticoagulants such as warfarin, acenocoumarol and phenprocoumon were standard treatment protocols [2, 3]. However these drugs have low therapeutic index, delayed onset of action, many drug-drug and drug-food interactions and difficult pharmacological management since they require a regular monitoring and adjustment [4, 5]. The development of DOACs has focused on eliminating these disadvantages associated with Vitamin K antagonists.

Few novel types of oral anticoagulants have recently been approved for use in the USA, Canada, the European Union, and several other countries. These are Dabigatran etexilate, Rivaroxaban, Edoxaban and Apixaban. In contrast to warfarin, these orally administered drugs approach anticoagulation by interfering with very specific, single, "targeted" steps in the coagulation cascade [6]. Unlike warfarin, dabigatran and rivaroxaban are reported to have comparatively few drug-drug interactions and no significant food interactions [7] and are able to provide stable anticoagulation at a fixed dose without the need for routine laboratory monitoring of coagulation (e.g., international normalized ratio [INR]) and associated dosage adjustments [6,8,9].

The DOACs exhibit a rapid onset of action (2-4 hours) and have relatively short half-lives (5-13 hours for rivaroxaban, ~12 hours for apixaban and ~13 hours for dabigatran, depending on renal function and age) [10,11,12]. Because of these

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pharmacokinetic properties, it is possible to modify an individual's anticoagulation status quite rapidly, minimising the period where the anticoagulation activity is therapeutically sub-optimal. Although in development, there are not any simple reversal agents available for the DOACs as yet [13]. However, the short half-lives of these drugs allow for the relatively rapid reduction of their anticoagulation effects.

The dental management of patients on oral anti-coagulant treatment should always be painstaking, and especially to those more invasive treatments that generate or can generate bleeding. The dentist must know the therapeutic range of the patient, according to the cardiovascular disease that he/she presents, and based on that; assess the potential risk of bleeding prior to dental treatment. In the case of dental procedures, the risk of thrombotic events due to altering or discontinuing antithrombotic therapy outweighs the low risk of potential perioperative bleeding complications among patients treated with single or dual antiplatelet therapy or Vitamin K antagonists.

Table 1: Postoperative bleeding risk for dental procedures. Reproduced from Scottish Dental Clinical Effectiveness Programme (SDCEP)

Dental procedures that are unlikely to cause bleeding	Dental procedures that are likely to cause bleeding	
	Low risk of postoperative bleeding complications	High risk of postoperative bleeding complications
Local anesthesia by infiltration, intraligamentary or mental nerve block. Local anesthesia by inferior dental block or regional nerve blocks Basic periodontal examination(BPE) Supragingival removal of plaque, calculus and stain Direct or indirect restoration with supragingival margins Endodontics- orthograde Impressions and other prosthetic procedures	Simple extraction(1-3 teeth, with restricted wound size Incision and drainage of intraoral swellings Detailed six point full periodontal examination Root surface instrumentation(RSI) and subgingival scaling Direct or indirect restorations with subgingival margins	Complex extractions, adjacent extractions that will cause a large wound or more than 3 extractions at once Flap raising procedures • Elective surgical extractions • Periodontal surgery • Periradicular surgery • Preprosthetic surgery • Crown lengthening • Dental implant surgery • Gingival recontouring • Biopsies

The use of oral anticoagulants is always controversial because of the low therapeutic index [14]; an excessive overdose is linked to the occurrence of haemorrhage, whereas if there is insufficient plasma concentration it increases the risk of thromboembolic phenomena. This situation requires continuous monitoring of INR (International Normal Ratio) previously. One of the most important advantages of dabigatran and rivaroxaban, compared to classical anticoagulants, is the lack of the need for continuous monitoring in order to maintain levels of anticoagulation [15], INR values, at all times in a certain range depending on the patient's cardiovascular disease. This does not mean that the management of patients with dabigatran and rivaroxaban does not require special attention. In terms of dental treatment to be done, there will be a number of local haemostatic measures to reduce the risk of bleeding. Currently there is no specific reduction protocol of the dabigatran dosage or the rivaroxaban for dental use. In this sense, more scientific evidence is needed to specify the dental management to new anticoagulants, although, according to scientific evidence it seems to be much easier due to the stability of INR that is achieved with these drugs.

PHARMACOKINETICS

Direct thrombin inhibitors (DTI) - These are a class of targeted anticoagulants that bind directly to thrombin and block its interaction with its substrates. The first orally administered DTI approved for use in USA is Dabigatran etexilate. Dabigatrin has been shown to be as effective as warfarin in prevention and treatment of recurrent venous thromboembolism and pulmonary embolism. Its mechanism of action is to bind with the active site on the thrombin molecule (Factor IIa) so that it cannot catalyze fibrinogen into fibrin. Unlike warfarin, dabigatran etexilate directly inhibits both free and clot-bound thrombin. Dabigatran is usually administered twice daily.

After oral administration, dabigatran etexilate (a pro- drug) is converted to dabigatran. Approximately 35% of dabigatran is bound to plasma proteins, and its terminal half-life is 12-14 hours (14-17 hours in the elderly). With twice-daily administration of dabigatran etexilate, plasma concentrations of dabigatran reached steady state within 2 to 3 days [16].

No specific antidote or reversal agent exists to counter the anticoagulant effect of dabigatran. However, owing to dabigatran's short half-life, merely discontinuing the administration of the drug is thought to be sufficient to resolve minor bleeding in most circumstances [17].

Factor Xa inhibitors- Orally administered FXaIs include rivaroxaban, apixaban, edoxaban, betrixaban, darexaban, and eribaxaban, and idrabiotaparinux is a parenteral FXaI. Among the FXaIs, only rivaroxaban is currently approved for use in humans and the site of activity for FXaIs is very specific in that they bind with the part of factor Xa that catalyzes the activation of factor II (prothrombin), so that no thrombin is present. Direct FXaIs can inhibit free factor Xa, clot-bound factor Xa, and factor Xa bound to the prothrombinase complex. Like dabigatran, rivaroxaban is also a substrate of P-gp transporters.

DENTAL CONSIDERATIONS

Because of the recent introduction of these drugs very less data can be found in the literature that offer specific recommendations for the management of dental patients taking these drugs.

A retrospective study by Hong *et al* reported that none of the 37 patients receiving LMWH (enoxaparin) as their only anticoagulant drug had any postoperative bleeding complications after the extraction of teeth [18]. In that study, all tooth extractions included the use of adjunctive hemostatic measures (i.e., absorbable gelatin compressed sponges [Gelfoam] and/or sutures) as indicated. Also in that study, enoxaparin was not discontinued before oral surgery procedures.

Romond *et al* [19] in 2013 concluded that in dental extractions under dabigatran there is no greater risk of bleeding but there should be a consensus between the dentist and the physician responsible for the patient regarding the management of the anticoagulant treatment.

Breik et al [4] in 2015 proposed that in general dental procedures like single dental extractions, periodontal treatment or root canal treatment there is no need to stop dabigatran.

If we look at studies that evaluate the effects of rivaroxaban, there are some differences regarding the postoperative bleeding risk between the articles reviewed. While Gómez Moreno *et al* [20] and Abayon *et al* [21] found that there was no difference in postoperative bleeding; Hanken *et al* [22] concluded that rivaroxaban has a higher risk of bleeding than other oral anticoagulants.

Based on these studies it does not appear that it would be necessary to discontinue the use of dabigatran or rivaroxaban before dental treatment likely to cause bleeding, including most uncomplicated tooth extractions, in most patients, especially if adjunctive local hemostatic measures (e.g., absorbable gelatin or oxidized cellulose sponges, sutures, local pressure [with sterile gauze pads moistened with water, normal saline solution, or 5% tranexamic acid solution], etc.) are used appropriately when indicated. However, in oral/maxillofacial surgical procedures with concerns for possible complications resulting from excessive bleeding and/or impaired hemostasis, dabigatran should be discontinued at least 24 hours before elective surgery, or longer, depending on the risk of bleeding based on the type and complexity of

the surgical procedure, the presence and degree of any renal impairment, and the presence of other risks for impaired hemostasis [23].

DRUG INTERACTIONS

These newer anticoagulant has fewer drug interactions. Rivaroxaban does not seem to inhibit or induce any P450 enzyme. The rivaroxaban shows no relevant drug interaction with non-steroidal antiinflammatory drugs (NSAIDs) contrary to what occurs with oral coumarin anticoagulants, which when combined lead to increased bleeding [24]. It has been suggested that rivaroxaban and enoxaparin can be admistered in concomitantly form or in sequential therapy [25]. Rivaroxaban prolongs the bleeding time when co-administered with aspirin or clopidogrel, although the relevance of this interaction is weak and does not affect platelet aggregation. Dabigatran, moreover, is not metabolized by the cytochrome P450 system and therefore presents a profile of drug without major problems of drug interactions. With regard to potential interactions with antimicrobials caution should be exercised only due to its pharmacokinetics, with clarithromycin and rifampicin. There is no specific antidote [26], so that in case of overdose should maintain adequate diuresis, haemostasis or the transfusion of fresh frozen plasma [25].

Table 2- Potential interactions of oral anticoagulants with drugs used or prescribed in dentistry [23].

RECOMMMENDATIONS	DABIGATRAN	RIVAROXABAN
Concurrent use not recommended	P-gp inducers, including carbamazepine, dexamethasone	Potent CYP3A4 and P-gp inhibitors, including itraconazole, ketoconazole, posaconazole, voriconazole
Concurrent use should be avoided if possible	P-gp inhibitors, including ketoconazole and possibly erythromycin, clarithromycin, itraconazole)	None
Use with caution	NSAIDs and salicylates	NSAIDs and salicylates Macrolide antibiotics (especially erythromycin and clarithromycin) Fluconazole Opioid analgesics

Simultaneous use of dabigatran and P-gp inhibitors, such as ketoconazole (and possibly itraconazole, erythromycin, and clarithromycin) should be avoided if possible. If simultaneous use of dabigatran and P-gp inhibitors is necessary, then a dose reduction of dabigatran may be indicated to reduce the potential risk of serious adverse events, including bleeding [27].

Hence, the simultaneous use of ketoconazole, itraconazole, voriconazole, and posaconazole is not recommended in patients being treated with rivaroxaban. Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.

Simultaneous use of dabigatran and NSAIDs (specifically diclofenac) does not appear to result in a clinically significant interaction, according to a study by Stangier [28]. Nevertheless, because non–

COX-selective NSAIDs (and salicylates) inhibit platelet aggregation and may cause gastrointestinal bleeding and peptic ulceration and/or perforation, it may be prudent to increase monitoring of the patient for signs and symptoms of bleeding if these drugs are used concomitantly, especially in the context of oral surgery procedures.

Based on this information, it would nevertheless appear to be prudent to use caution if an NSAID or opioid analgesic is to be used concomitantly with rivaroxaban and to increase monitoring of the patient for signs and symptoms of bleeding, especially in the context of oral surgery procedures.

CONCLUSION

Various investigations regarding the new oral anticoagulants (Dabigatran and rivaroxaban) are showing clear benefits to these targeted oral anticoagulants over the older, but less costly, warfarin and these DOACs are relatively safe drugs in terms of bleeding. Removal of the anticoagulant 24 hours before the procedure appears to be an adequate approach that has increased risk of thromboembolic events. However, when dental procedures are performed without withdrawal of the drug the bleeding is manageable with conventional haemostasis measurements.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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