MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

Beyond warfarin: the new generation of oral anticoagulants and their implications for the management of dental patients

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Warfarin has been the primary anticoagulant drug used in the USA for more than 50 years. However, 2 novel types of oral anticoagulants have recently been approved for use in the USA. These are direct thrombin inhibitors (e.g., dabigatran etexilate) and factor Xa inhibitors (e.g., rivaroxaban). Dental health care providers may soon encounter patients who are being prescribed these medications. This article describes the pharmacologic properties and medical uses of these new oral anticoagulants. Also discussed are implications for the management of dental patients being treated with these new oral anticoagulants, including potential interactions with drugs commonly used or prescribed in the course of dental treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:431-441)

Various diseases and medical conditions can require treatment that includes the use of extended-duration (i.e., ~4 weeks or longer) anticoagulant drug therapy.[1] Among these are:

- Prophylaxis (prevention) and treatment of pulmonary embolism (PE) and venous thrombosis, i.e., venous thromboembolism (VTE) and deep vein thrombosis (DVT), including thromboprophylaxis for the prevention of postoperative VTE after orthopedic surgical procedures, including hip fracture and prosthetic total hip or knee joint replacement.
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or prosthetic replacement of cardiac valves.
- Reduction of the risk of death, reinfarction, and thromboembolic events, such as stroke or systemic embolization after myocardial infarction.

Although parenterally administered anticoagulants can be used for extended durations, the potential advantages and convenience of orally administered anticoagulant therapy in terms of improving patient adherence to therapy are clearly evident.[2] Also, orally administered anticoagulant therapy is generally more cost-effective, even when compared to outpatient subcutaneous anticoagulant drug administration, as is required with low-molecular-weight heparin (LMWH).[3]

In the USA, the mainstay for anticoagulant therapy for more than 50 years is warfarin. Warfarin ranks among the most commonly prescribed drugs on the market, with >2 million individuals in the USA and 1 million individuals in the UK estimated to be taking warfarin. In the USA, >300,000 new patients are prescribed warfarin each year.[4,5] From 1998 to 2004 the number of outpatient prescriptions dispensed for warfarin in the USA increased 1.45-fold from 21.1 million to 30.6 million.[6]

Warfarin is a coumarin-derivative orally administered anticoagulant that is classified as a vitamin K antagonist (VKA). Other, less commonly used, VKA anticoagulants include acenocoumarol, phenprocoumon, and phenindione. For the past 60 years, coumarin-derivative VKAs have been the only generally available option for an orally administered anticoagulant drug.[2,7]

TARGETED ANTICOAGULATION AND NEW ORAL ANTICOAGULANTS

The development of new orally administered anticoagulant drugs over the past few years has focused on eliminating some of the disadvantages associated with warfarin. Compared with warfarin, the next generation of orally administered anticoagulants would ideally have a wide therapeutic index, less complex pharmacodynamics, few drug-drug and food interactions, and produce such a

Statement of Clinical Relevance

This manuscript reviews the pharmacologic properties and medical uses of two new oral anticoagulants (dabigatran and rivaroxaban). Also discussed are implications for the management of dental patients being treated with these oral anticoagulants, including potential interactions with drugs commonly used or prescribed in the course of dental treatment.

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Received for publication Jun 28, 2011; returned for revision Sep 17, 2011; accepted for publication Oct 13, 2011.

2212-4403/$ - see front matter
doi:10.1016/j.oooo.2011.10.005

Table 1. Pharmacologic properties of oral anticoagulants

	Warfarin	*Dabigatran*	*Rivaroxaban*
Target(s)	Factors II, VII, IX, and X, proteins C and S	Thrombin	Factor Xa
Oral bioavailability	~100%	3%-7%	80%-100%
Typical dosing schedule for thromboprophylaxis	Daily	Twice daily	Daily
Time to peak plasma concentration (T_{max})	2-8 h (mean ~4 h)	2.0-4.0 h	2.5-4 h
Effective half-life ($T_{1/2}$)	20-60 h (mean ~40 h)	Adult: 12-17 h; elderly: 14-17 h; mild-to-moderate renal impairment: 15-18 h; severe renal impairment: 28 h	Young individual: 5-9 h; elderly: 11-13 h
Metabolism	Hepatic primarily via CYP2C9; minor pathways include CYP2C8, CYP2C18, CYP2C19, CYP1A2, and CYP3A4	Primarily by esterase-catalyzed hydrolysis in the plasma or liver	Hepatic via CYP3A4, CYP3A5, and CYP2J2
Elimination	Up to 92% renal (urine)	Urine: 80%-85%	Urine: 66% (36% as unchanged drug, 30% as inactive metabolites); feces: 28% (mostly as inactive metabolites)
Food interference with absorption	May delay the rate, but not the extent of absorption	Acidic environment required so absorption may be reduced by foods or drugs that increase the pH of the stomach and small intestine (e.g., proton pump inhibitors)	Increases rate and extent of absorption by 25%-35%
Need for routine monitoring of coagulation	Yes (INR)	No	No

predictable anticoagulant response at fixed doses that routine coagulation monitoring is unnecessary.[1,2]

Two 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 (a direct thrombin inhibitor [DTI]) and rivaroxaban (a factor Xa inhibitor [FXaI]).

In contrast to warfarin, both orally administered DTIs (e.g., dabigatran etexilate) and FXaIs (e.g., rivaroxaban) approach anticoagulation by interfering with very specific, single, "targeted" steps in the coagulation cascade (similar to those of subcutaneously or intravenously administered LMWH [e.g., enoxaparin]).[8] They are relatively small molecules with comparatively rapid onsets of action and short half-lives. Unlike warfarin, dabigatran and rivaroxaban are reported to have comparatively few drug-drug interactions and no significant food interactions[9] 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.[8,10,11] Table I summarizes the pharmacologic properties of warfarin, dabigatran, and rivaroxaban.

It is also possible that one or more of these DTIs or FXaIs has a wider therapeutic index than warfarin, thus reducing the risk of hemorrhage while preserving the beneficial antithrombotic effects. However, at least some of the initial clinical trials of these anticoagulants involving thromboprophylaxis in postorthopedic surgery patients suggest that there will continue to be a tradeoff (i.e., fewer thromboembolic events will be balanced by excessive bleeding, and vice versa).[12]

DIRECT THROMBIN INHIBITORS: DABIGATRAN

DTIs are a class of targeted anticoagulants that bind directly to thrombin and block its interaction with its substrates.[30] Bivalent DTIs (derived from hirudin, the naturally occurring peptide in the salivary glands of medicinal leeches) include bivalirudin, desirudin, and lepirudin, although the univalent DTIs include argatroban and dabigatran.[13]

The first orally administered DTI approved for use in the USA is dabigatran etexilate. It received Food and Drug Administration (FDA) approval in October 2010 after good success with desirudin, a parenteral DTI.[14] The initial FDA approved indication of dabigatran etexilate is to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, but it is also being used for postsurgical thromboprophylaxis with

prosthetic knee and hip joint replacement patients in Canada, the European Union, and several other countries.[14,15] Dabigatran, compared with warfarin, was shown to have superior safety with equivalent efficacy for the prevention of stroke in patients with atrial fibrillation.[16] Dabigatran has also been shown to be as effective as warfarin in prevention and treatment of recurrent venous thromboembolism and pulmonary embolism.[17]

Dabigatran etexilate's 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.[8]

Dabigatran etexilate is usually administered twice daily. The absolute bioavailability following oral administration of dabigatran etexilate is ~3%-7%, and it has a fairly rapid onset of action, with maximum plasma concentration occurring 2.0-4.0 hours (median 3.0 hours) after administration.[18,19] Dabigatran etexilate is poorly soluble at pH >4, and coadministration with a proton pump inhibitor (specifically, pantoprazole) that increases gastric pH to neutral levels, was reported to decrease dabigatran bioavailability.[9]

After oral administration, dabigatran etexilate (a prodrug) 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.[18] When administered intravenously, dabigatran is eliminated unchanged primarily (80%-85%) in the urine, however, after oral administration of radiolabeled dabigatran etexilate, 7% of radioactivity is recovered in urine and 86% in feces owing to the drug's low oral bioavailability.[20] Dabigatran acts as a substrate of the efflux transporter P-glycoprotein (P-gp) and is primarily metabolized by esterase-catalyzed hydrolysis in the plasma or liver. Dabigatran is not a substrate, inhibitor, or inducer of hepatic cytochrome P-450 (CYP).[9]

In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study,[16] the most frequently reported (>15% of patients) adverse effects associated with dabigatran were gastritis-like symptoms, including dyspepsia, abdominal discomfort/pain, and epigastric discomfort. Minor bleeding events were reported in 8%-33% of patients and major bleeding events (i.e., gastrointestinal hemorrhage) in ≤6% of patients.

Unlike the anticoagulant effect of warfarin, which can be reversed by the administration of parenteral (or oral) vitamin K, or heparin/LMWHs, which can be reversed by the administration of parenteral protamine sulfate,[10] no such 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.[21] Supportive strategies to control more severe bleeding associated with dabigatran include mechanical compression, surgical hemostasis, fluid replacement, and transfusion of blood products (packed red cells or fresh frozen plasma). If these measures fail to control bleeding, then recombinant activated factor VII (rFVIIa) and/or hemodialysis can be considered.[21]

Dabigatran prolongs the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and thrombin time (TT) at recommended therapeutic doses, but it has little effect on prothrombin time (PT)/INR at clinically relevant plasma concentrations.[21,22]

As previously noted, routine coagulation monitoring is not required for patients being maintained on dabigatran.[8,10] Although both TT and ECT tests are the most sensitive tests for quantifying the anticoagulant effects of dabigatran, van Ryn et al.[21] suggests that in emergency situations, aPTT and/or TT would usually be the most accessible methods for monitoring the anticoagulant effects of dabigatran, because the ECT test (based on snake venom) is not widely available (and not currently FDA approved). In contrast, Castellone and van Cott[22] maintain that for monitoring the anticoagulant effect of DTIs (including dabigatran), TT is too sensitive, and the test result prolonged to >200 seconds; therefore, they recommend the use of aPTT (owing to its broad availability), as well as ECT or prothrombinase-induced clotting time assay when accessible.

FACTOR Xa INHIBITORS: RIVAROXABAN

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.[8]

Orally administered FXaIs include rivaroxaban, apixaban, edoxaban, betrixaban, darexaban, and eribaxaban, and idrabiotaparinux is a parenteral FXaI.[23] Among the FXaIs, only rivaroxaban is currently approved for use in humans, and apixaban appears to be in the most advanced stages of development and is in phase III clinical trials for the prevention of thrombosis-related events in patients undergoing knee arthroplasty[24] and the prevention of thromboembolism in patients with atrial fibrillation.[25]

Rivaroxaban is an orally administered, selective, reversible, direct FXaI that has been approved for use in the European Union, Canada, and several other countries for the prevention of VTE and pulmonary embolism in patients undergoing major orthopedic surgery of

the lower limbs, such as prosthetic joint replacement.[8,23] On July 1, 2011, rivaroxaban received FDA approval in the USA for the prevention of DVT in patients undergoing knee or hip replacement surgery.[26] The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) large clinical trial investigated the effectiveness of rivaroxaban compared with warfarin in the reduction of the incidence of ischemic stroke or systemic embolism in patients with atrial fibrillation.[27] However, the September 8, 2011, FDA briefing document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) recommended against approval of rivaroxaban for the prevention of stroke in atrial fibrillation patients, based on "a lack of substantial evidence that rivaroxaban will have its desired effect when used as recommended in labeling," primarily based on the FDA's analysis of data from the ROCKET-AF clinical trial.[28]

Rivaroxaban is usually administered once daily and shows a rapid onset of 2.5-4 hours (mean ~3 h). Once at steady state, the terminal half-life is 5.7-9.2 hours (up to 12-13 hours in patients >75 years old, apparently owing to decreased total and renal clearance).[12] Oral bioavailability is 80%-100%, and plasma protein binding is ~92%-95%.[8] Approximately 51% of rivaroxaban undergoes metabolic degradation.[29,30] Rivaroxaban does not inhibit or induce any major CYP enzymes, but two-thirds of the drug is metabolized by CYP3A4, CYP3A5, CYP2J2, and CYP-independent mechanisms before elimination.[29,30] Like dabigatran, rivaroxaban is also a substrate of P-gp transporters.[9] After oral administration, 66% of a dose of rivaroxaban is excreted in urine, mainly via active tubular secretion (36% as the unchanged drug, 30% as inactive metabolites), and 28% in the feces (21% as inactive metabolites, 7% as the unchanged drug).[29,30]

The most frequent adverse effects associated with the use of rivaroxaban are minor bleeding events in 4%-7% of patients, major bleeding events in events in <1%-2% of patients (including postsurgical site bleeding events associated with decreased hemoglobin or requiring transfusion), and gastrointestinal (nausea) in 1% of patients.[23]

There is no specific reversal agent or antidote for rivaroxaban, but its short half-life means that the discontinuation of the drug is likely be adequate to correct most bleeding problems caused by its use. Blood product or component transfusion, or administration of rFVIIa or prothrombin complex concentrate, may be considered in cases of severe or life-threatening bleeding due to rivaroxaban.[29-31]

FXaIs, including rivaroxaban, are reported to slightly prolong PT and aPTT.[22] The test that is reported to be best able to monitor the anticoagulant effect of FXaIs (as well as LMWH) is an anti–factor Xa assay[22]; however, no routine laboratory test monitoring of coagulation should be required for patients receiving rivaroxaban, except possibly in special circumstances, such as renal failure, obesity, or severely underweight patients.[8,11,32]

DENTAL MANAGEMENT CONSIDERATIONS

Dental patients who are taking an orally administered anticoagulant frequently have serious medical conditions (e.g., atrial fibrillation, ischemic heart disease, prosthetic cardiac valve) necessitating the use of anticoagulant therapy and that must be identified and addressed by the dental health care provider before invasive dental treatment is initiated. Table II summarizes the management of dental patients being treated with oral anticoagulants (warfarin, dabigatran, and rivaroxaban).

The management of patients receiving warfarin who require invasive dental procedures that involve bleeding and/or oral and maxillofacial surgery is well documented in the literature.[33-40] In contrast, no clinical trials or evidence-based data can be found in the literature that offer specific recommendations for the management of dental patients, such as those requiring oral surgery, who are receiving dabigatran or rivaroxaban, presumably owing to the relatively recent approval of these drugs for use in the general patient population. However, we infer that the management of dental patients, particularly those requiring oral surgery, who are receiving dabigatran or rivaroxaban would be essentially equivalent to recommendations reported in the literature for patients receiving these drugs who require elective minor surgical procedures where bleeding is likely to occur,[21] and it would be most analogous to recommendations for patients receiving other, comparable anticoagulants, specifically LMHW (e.g., enoxaparin), who require oral surgery, owing to the similarities in pharmacologic properties (especially half-life) seen with LMWH, FXaIs, and DTIs.

Only 2 studies in the English-language literature could be found that report the frequency of bleeding and related complications after oral surgery (i.e., tooth extractions) in patients receiving LMWH.[41,42] In a randomized, prospective trial comparing bridging therapy using LMWH with maintenance of oral anticoagulation with warfarin during the extraction of teeth,[41] of the 104 patients receiving LMWH (which was subsequently discontinued ≥12 h before tooth extraction), only 5 patients (4.76%) exhibited significant postextraction bleeding. All 5 cases of hemorrhage were easily resolved with local hemostatic measures, and in 3 of these cases a local hemostatic agent (reabsorptive collagen sponge) was used. A retrospective study by Hong[42] et al. reported that none of the 37 patients

Table II. Summary of the management of dental patients taking oral anticoagulants

	Warfarin	*Dabigatran*	*Rivaroxaban*
Best laboratory test(s) to assess drug's effect on hemostasis	PT/INR	ECT, TT, aPTT	Anti–factor Xa assay (preferred) PT/INR and/or aPTT*
Guidelines for the management of dental procedures that involve bleeding, (including most uncomplicated tooth extractions)	Patients who require oral surgery or dental treatment likely to cause bleeding (including uncomplicated tooth extractions) typically do not require alteration of their warfarin therapy regimen unless their INR is greater than an upper limit range of 3.5-4.0, provided that adjunctive local hemostatic measures† are used when indicated[33-40]	It does not appear that it is necessary to discontinue the use of dabigatran in patients with normal renal function and without other risks for impaired hemostasis, especially if adjunctive local hemostatic measures† are used when indicated	It does not appear that it is necessary to discontinue the use of rivaroxaban in patients with normal renal function and without other risks for impaired hemostasis, especially if adjunctive local hemostatic measures† are used when indicated
Guidelines for the management of oral/maxillofacial surgery procedures with concerns of possible complications resulting from excessive bleeding and/or impaired hemostasis	Discontinue warfarin typically 2-3 d before surgery^{-}	Discontinue dabigatran ≥24 h before surgery, or longer depending on the presence and degree of renal impairment and bleeding risk (see Table III)	Discontinue rivaroxaban ≥24 h prior to surgery, or longer depending on the presence and degree of renal impairment and bleeding risk
Antidote/reversal agent available	Yes (vitamin K)	No	No

aPTT, activated partial thromboplastin time; *ECT,* ecarin clotting time; *PT/INR,* prothrombin time/international normalized ratio; *TT,* thrombin time.

*Although rivaroxaban may slightly prolong PT/INR and aPTT, it does not appear that these tests would be clinically useful in assessing the anticoagulant effect produced by the drug.

†Adjunctive local hemostatic measures include absorbable gelatin or oxidized cellulose sponges, sutures, local pressure (with sterile gauze pads moistened with water, normal saline, or 5% tranexamic acid solution).

receiving LMWH (enoxaparin) as their only anticoagulant drug had any postoperative bleeding complications after the extraction of teeth. 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.

Additionally, the best available recommendations concerning the discontinuation of dabigatran prior to elective general surgery appear to be those by van Ryn et al.[21] (summarized in Table III). Based on data reporting postextraction bleeding in patients receiving LMWH[41,42] and the recommendations of van Ryn et al.[21] regarding the discontinuation of dabigatran before elective general surgery, we would not expect there to be a significant risk for serious bleeding complications after dental treatment, including most uncomplicated tooth extractions, for patients with normal renal function being treated with dabigatran (or rivaroxaban) in the absence of any other risks for impaired hemostasis. Therefore, 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 situations where oral/maxillofacial surgical procedures may require the temporary discontinuation of dabigatran owing to 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 as outlined in (Table III).[21]

Patients with renal impairment or insufficiency, as indicated by increased serum creatinine and decreased creatinine clearance and estimated glomerular filtration rate, are reported to have a higher maximum plasma concentration of orally administered dabigatran, as well as longer half-life and increased bleeding risk,[21,30,36] and therefore require additional time of discontinuation of dabigatran before surgery, as outlined in Table III. Additionally, the patient prescribing information for dabigatran notes an increased bleeding risk among those older than 75 years.[19]

For patients undergoing elective dental surgery where complications due to increased bleeding/impaired hemo-

Table III. Guide to the discontinuation of dabigatran before elective surgery in patients receiving once or twice daily dosing with a standard or high risk of bleeding[21]

Renal function (creatinine clearance, mL/min)	*Dabigatran half-life (h)**	*Timing of discontinuation after last dose of dabigatran before surgery*	
		Standard risk of bleeding	*High risk of bleeding†*
>80	13 (11-22)	24 h	2-4 d
>50 to ≤80	15 (12-34)	24 h	2-4 d
>30 to ≤50	18 (13-23)	≥48 h	4 d
≤30‡	27 (22-35)	2-5 d	>5 d

*Data from renal impairment study in healthy volunteers,[78] geometric mean (range).

†Types of surgery associated with a high risk of bleeding (or in major surgery where complete hemostasis may be required) include, but are not limited to, cardiac, neural, abdominal, and those involving a major organ. Other procedures, such as spinal anesthesia, may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, comorbidities (e.g., major cardiac, respiratory, or liver disease) and concomitant use of antiplatelet therapy.

‡Dabigatran is contraindicated for use in these patients.

stasis indicate the discontinuation of dabigatran, a TT and/or aPTT could be performed 6-12 hours before surgery, and a normal result, as defined by the local laboratory, would be indicative that the anticoagulant effect produced by dabigatran has abated.[21,22]

Similar guidelines would appear to be applicable for patients taking rivaroxaban and undergoing oral/maxillofacial surgical procedures, with the recommendation of discontinuing the drug at least 24 hours before elective surgery if there are concerns regarding the possibility of excessive bleeding and/or impaired hemostasis.[43] It should be noted that patients with severe renal insufficiency (specifically, creatinine clearance of ≤29 mL/min) are reported to have significantly increased maximum plasma concentration and longer half-life of orally administered of rivaroxaban, which may necessitate a longer period of time (>24 h) of discontinuation of the drug before surgery.[8,23,29] Owing to the minimal effect of rivaroxaban in prolonging PT and aPTT, it does not appear that these tests (or any other commonly available coagulation test) would be clinically useful in assessing the anticoagulant effect produced by the drug.[22]

Administration of dabigatran or rivaroxaban should not be restarted after oral/maxillofacial surgical procedures until the risk of postoperative bleeding is minimal (i.e., after a stable fibrin clot is formed), usually within 24-48 hours following surgery, because the onset of the anticoagulant effect of these drugs is rapid (compared with warfarin).

INTERACTIONS WITH DRUGS FREQUENTLY USED OR PRESCRIBED IN DENTISTRY

Owing to the short amount of time that both dabigatran and rivaroxaban have been approved for use in humans, "real-world" experience with drug interactions in patients being treated with these drugs, especially on a long-term basis, is lacking compared with drug interaction data that has been complied for warfarin. The potential for pharmacogenetic alterations to alter the pharmacokinetics and/or pharmacodynamics of these new oral anticoagulants, as well as to affect interactions of these drugs with other drugs and food supplements, has yet to be determined.[9]

Warfarin

Warfarin is a racemic mixture of R (weak) and S (potent) anticoagulant enantiomers. Warfarin is biotransformed into inactive metabolites by hepatic CYP, specifically, CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4.[44,45] S-Warfarin is biotransformed into inactive metabolites primarily by CYP2C9, whereas R-warfarin is biotransformed by CYP1A2 (major pathway) and CYP2C19 and CYP3A4 (minor pathways).[44,45]

Because the S-enantiomer of warfarin is ~2-5 times more potent than R-warfarin, drugs that preferentially alter (i.e., increase or decrease) the metabolism of S-warfarin are more likely to be associated with alterations in INR.[44,46] Therefore, there is a risk of increased bleeding and hemorrhage in patients concomitantly taking warfarin and other drugs(s) that may decrease warfarin metabolism, especially those that do so via CYP2C9 inhibition.[47,48]

Some drugs that are commonly used in dentistry and reported to significantly interact with warfarin via CYP inhibition are azole antifungals, including ketoconazole,[49] fluconazole,[50,51] and to a lesser degree itraconazole[52] and metronidazole.[53,54] Additionally, trimethoprim-sulfamethoxazole has been reported to significantly increase the anticoagulant effect of warfarin within a few days of the initiation of its use in patients.[55,56] Although it is thought that CYP2C9 inhibition by sulfamethoxazole may play a role in this interaction with warfarin, its mechanism has not been clearly established and appears to be multifactorial.

Macrolide antibiotics (i.e., erythromycin,[57] clarithromycin,[58] and possibly azithromycin[59]) have been implicated in causing significant episodes of bleeding in patients taking warfarin. A proposed mechanism for this interaction is the inhibition of CYP3A4 by macrolides which metabolizes the less potent R-enantiomer of warfarin.

Other drugs used or prescribed in the course of dental treatment that, when use concomitantly with warfarin,

may increase the risk for bleeding and hemorrhage, but appear to do so pharmacodynamically rather than significantly attributed to CYP inhibition, include nonsteroidal antiinflammatory agents (NSAIDs) and acetaminophen.[48]

Non–COX-selective NSAIDs (including, but not limited to, aspirin, diflunisal, flurbiprofen, ibuprofen, naproxen, and ketoprofen) should be used with caution in patients receiving warfarin.[60,61] These drugs inhibit platelet aggregation and may cause GI bleeding and peptic ulceration and/or perforation. Increased bleeding may occur during concomitant NSAID therapy with warfarin independently of an increase in INR, therefore, it is recommended to monitor the patient for increased signs and symptoms of bleeding if these drugs are used concomitantly.

The question of a potential interaction between warfarin and acetaminophen is one that remains controversial owing to conflicting data in the literature. While much of the earlier published reports investigating a potential interaction between acetaminophen and warfarin were based on observational data or case-control studies, a randomized, double-blind, controlled study in 2003 by Gadisseur et al.[62] did not reveal clinically significant changes in INR of patients taking warfarin after sustained use of acetaminophen.

However, more recent randomized controlled studies suggest that potential clinically significant interaction between warfarin and acetaminophen may be more important than previously thought, including those by Mahé et al.,[63] Parra et al.,[64] and Zhang et al.,[65] which all reported an enhanced anticoagulant effect with clinically significant increased INR in patients receiving concomitant warfarin and acetaminophen. Recommendations based on data from these studies suggest that close INR monitoring (i.e., every 3-5 days) is advised in patients taking acetaminophen daily during warfarin therapy, especially in those patients with INR values close to the upper target range, and/or patients that are expected to take, or have been taking, >1.3 g/d acetaminophen for >1 week, because warfarin dosage adjustment may be necessary in these patients.

Other drugs used or prescribed in the course of dental treatment that may enhance the hypoprothrombinemic effect of warfarin include tetracyclines (especially doxycycline or tetracycline),[66,67] cephalosporins,[68] and levofloxacin.[69,70] The mechanism of the interaction between warfarin and these antibiotics remains uncertain. Postulated mechanisms include an antibiotic-induced reduction in prothrombin activity (hypoprothrombinemia) and a reduction in gastrointestinal bacteria flora essential for vitamin K production which is subsequently used to produce various clotting factors. Conversely, dicloxacillin has been reported to decrease INR to subtherapeutic values in patients receiving warfarin; the mechanism of this interaction is unknown.[71,72] Potential interactions with warfarin and these antibiotics appear to occur relatively infrequently and/or to be of limited clinical significance, resulting in only minor increases in INR. Nevertheless, close monitoring of INR is may be advisable when patients are prescribed any of these antibiotics while concomitantly receiving warfarin.

Dabigatran

Dabigatran acts as a substrate of the efflux transporter P-gp; therefore, it appears that use of dabigatran concomitantly with strong P-gp inducers is generally not recommended, while the use of dabigatran concomitantly with P-gp inhibitors should be avoided if possible.[8,9]

Strong P-gp inducers (specifically rifampin, but also possibly other P-gp inducers, such as dexamethasone and carbamazepine) have been reported to significantly decrease the plasma concentration–versus-time curve (area under the receiver operating characteristic curve [AUC]) and peak serum concentration (C_{max}) of dabigatran, and their concomitant use with dabigatran is generally not recommended.[19]

The P-gp inhibitor ketoconazole was reported to significantly increase AUC and C_{max} of dabigatran. Dabigatran AUC and C_{max} were increased an average of 138% and 135%, respectively, when given after a single dose (400 mg) of ketoconazole.[19] In contrast, concomitant therapy with clarithromycin (a moderate P-gp inhibitor) resulted in an insignificant effect on dabigatran concentrations, with AUC and C_{max} increased an average of only 15% and 19%, respectively.[73] Therefore, it seems to be prudent that concomitant use of dabigatran and P-gp inhibitors, such as ketoconazole (and possibly itraconazole, erythromycin, and clarithromycin) should be avoided if possible. If concomitant 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.

The concomitant use of dabigatran and NSAIDs (specifically diclofenac) does not appear to result in a clinically significant interaction, according to a study by Stangier.[74] In that study, the concomitant administration of dabigatran and a single dose (50 mg) of diclofenac to healthy young subjects ($n = 24$) reduced the bioavailability of diclofenac and its metabolite as measured by plasma AUC and C_{max}, but the same pharmacokinetic parameters of dabigatran were unaffected. 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.

Two-thirds of the rivaroxaban is metabolized by CYP3A4, CYP3A5, CYP2J2, and CYP-independent mechanisms before elimination, and rivaroxaban also is a substrate of P-gp transporters. Therefore, the concomitant use of rivaroxaban with drugs that are strong inhibitors of both CYP3A4 and P-gp is not recommended.[9,29,30]

According to the rivaroxaban prescribing information,[29,30] coadministration of rivaroxaban with ketoconazole (400 mg, once daily) led to a 2.6-fold increase in mean rivaroxaban AUC and a 1.7-fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects that may lead to an increased bleeding risk.

Therefore, the concomitant use of strong inhibitors of both CYP3A4 and P-gp, including systemic azole-antimycotics, such as ketoconazole, itraconazole, voriconazole, and posaconazole (as well as human immunodeficiency virus protease inhibitors) is not recommended in patients being treated with rivaroxaban. Fluconazole is expected to have less effect on rivaroxaban exposure and can be coadministered with caution.

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin is considered a strong CYP3A4 inhibitor and moderate P-gp inhibitor, and a 500 mg twice-daily dose led to a 1.5-fold increase in mean rivaroxaban AUC and a 1.4-fold increase in C_{max}. This increase was not considered to be clinically relevant.[75] Erythromycin inhibits CYP3A4 and P-gp moderately. A 500 mg 3 times per day dose of erythromycin led to a 1.3-fold increase in mean rivaroxaban AUC and C_{max}. This increase was not considered to be clinically relevant.[75]

Regarding potential interactions between NSAIDs and rivaroxaban, a study by Kubitza et al.[76] concluded that there appears to be no clinically relevant interaction between rivaroxaban and naproxen (500 mg/d) in the 11 healthy male subjects aged 18-45 years enrolled in their study, although some individuals may be more sensitive to the combination of these drugs. That study reported the extent of inhibition of factor Xa activity, and prolongation of PT and aPTT were not significantly affected, although time to achieve maximum effect was delayed. Although platelet aggregation was reported to be unaffected, concomitant use of rivaroxaban and naproxen significantly increased bleeding time compared with rivaroxaban alone ($P = .017$).

In the RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE) studies, 1 death was attributed to the combined effect of rivaroxaban and naproxen.[77] An analysis by the FDA of patients enrolled in the RECORD studies revealed that 36% of patient time (relative rate 1.28, 95% confidence interval [CI] 0.94-1.73) while comedicated (i.e., from the start of comedication up to 2 days after comedication discontinuation) with rivaroxaban and an NSAID experienced major or nonmajor clinically relevant postsurgical bleeding (MNCRB) compared with those who received rivaroxaban alone.[82] In comparison, only 5% of patient time (relative rate 1.11, 95% CI 0.55-2.25) while comedicated with platelet aggregation inhibitors or aspirin experienced MNCRB. Interestingly, patients comedicated with an opioid experienced an even higher rate of MNCRB (39% of patient time, relative rate 1.72, 95% CI 1.71-3.71) than those comedicated with an NSAID.[77] Additionally, the analysis by the FDA of patients enrolled in the RECORD studies noted that increased bleeding time (approximately doubled) after concomitant administration of rivaroxaban and aspirin or naproxen was observed, but they stated that this did not appear to be clinically relevant.[77]

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 patent for signs and symptoms of bleeding, especially in the context of oral surgery procedures.

The potential drug interactions with warfarin, dabigatran, and rivaroxaban and drugs used or prescribed in dentistry are summarized in Table IV.

CONCLUSION

The new oral anticoagulants (dabigatran and rivaroxaban) are seeing increased use in the USA and the European Union. Many investigations are showing clear benefits to these targeted oral anticoagulants over the older, but less costly, warfarin. However, the question of whether these new oral anticoagulants will ever replace, or become more widely used than, warfarin is one that remains to be answered.

For patients being treated with one of these new oral anticoagulants, the amount of "real-world" data and experience regarding their dental treatment implications and the management of patients undergoing dental procedures that are likely to involve significant bleeding is currently lacking. Clearly, clinical studies are needed to determine the effects that the new oral DTIs and FXaIs have on bleeding and hemostasis after tooth extractions and other surgical dental procedures.

Based on the information and data available at this time, we suggest that the management of patients taking dabigatran or rivaroxaban and undergoing dental

Table IV. Potential interactions of oral anticoagulants with drugs used or prescribed in dentistry

	Warfarin	*Dabigatran*	*Rivaroxaban*
Concurrent use not recommended	None	P-Glycoprotein inducers, including carbamazepine, dexamethasone	Potent CYP3A4 and P-glycoprotein inhibitors, including itraconazole, ketoconazole, posaconazole, voriconazole
Concurrent use should be avoided if possible	• Azole antifungals (e.g., fluconazole, ketoconazole) • Metronidazole • Sulfamethoxazole • NSAIDs and salicylates (including, but not limited to, aspirin, diflunisal, flurbiprofen, ibuprofen, naproxen, ketoprofen)	P-Glycoprotein inhibitors, including ketoconazole and possibly erythromycin, clarithromycin, itraconazole)	None
Use with caution	• Acetaminophen (most likely with daily doses >1.3 g for >1 wk) • Macrolide antibiotics (especially erythromycin and clarithromycin) • Tetracyclines • Levofloxacin • Cephalosporins	NSAIDs and salicylates	• NSAIDs and salicylates • Macrolide antibiotics (especially erythromycin and clarithromycin) • Fluconazole • Opioid analgesics

treatment or oral/maxillofacial surgical procedures should include the following.

Consult with the patient's physician regarding the planned dental or oral/maxillofacial surgical procedures and the possible need to discontinue dabigatran/rivaroxaban before surgery.

For dental procedures that involve bleeding (including most uncomplicated tooth extractions), it does not appear that it would be necessary to discontinue the use of dabigatran/rivaroxaban in patients with normal renal function, and without other risks for impaired hemostasis, especially if adjunctive local hemostatic measures are used appropriately when indicated.

In situations where oral/maxillofacial surgical procedures may require the temporary discontinuation of dabigatran because of concerns of possible complications resulting from excessive bleeding and/or impaired hemostasis, dabigatran/rivaroxaban 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.

Before surgery, an aPTT and/or TT (for patients taking dabigatran) or an anti–factor Xa assay (preferred), PT/INR, and/or aPTT (for patients taking rivaroxaban) can be ordered to provide an indication of anticoagulation due to these drugs.

Primary closure and the use of adjunctive local hemostatic measure is recommended for surgical procedures when possible.

Administration of dabigatran/rivaroxaban should not be restarted after oral/maxillofacial surgical procedures until the risk of postoperative bleeding is minimal (usually within 24-48 h after surgery).

If postsurgical bleeding occurs, contact the patient's physician, discontinue dabigatran/rivaroxaban, and:

For patients taking dabigatran, transfuse with packed red cells or fresh frozen plasma and consider hemodialysis and/or rFVIIa in severe or continued bleeding.

For patients taking rivaroxaban, transfuse with packed red cells or fresh frozen plasma and administer prothrombin complex concentrate or rFVIIa if available.

Hopefully, new data gathered from the wider use of these new oral anticoagulants (as well as reports and studies of interactions with concomitant medications) will yield more information that can be used to guide dental health care providers to provide safe care with or without modifications to these anticoagulants, as well as in the prescribing of dental therapeutic medications. Special attention appears to be needed to assure the safety of the concomitant use of NSAIDs and opioid analgesics that may prolong bleeding with some of these new anticoagulants; additional studies are clearly necessary.

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