DENTAL IMPLICATIONS OF THE NEW ORAL ANTICOAGULANTS

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ABSTRACT

Background: Patients treated with anticoagulants drugs have raised various issues between general dentists who have to balance between the bleeding risk and the thromboembolic risk. **Objectives**: The purpose of these paper is to review the new oral anticoagulants and to evaluate the implications referred to dental care. **Methods**: The primarily literature was consulted from product monographs and the medical literature in the electronic database through PubMed and Medscape. **Results**: Newer oral anticoagulants are associated with less bleeding than warfain. Most authors agree that the thromboembolic risk due to withdrawal of oral anticoagulants outweighs the risk of bleeding and in most of the cases they recommend the dental procedures without discontinuing the doses. Additionally, most bleeding complications can be controlled with local haemostatic measures. **Conclusion:** Dental management in patients under new oral anticoagulants is safer and easier because of their predictable and stable anticoagulant effect, less hemorrhage risk and lower drug interaction.

Key words: dental procedures, dabigatran, rivaroxaban, apixaban, oral bleeding

BACKGROUND

The prevalence of patients with cardiovascular and cerebrovascular chronic diseases is increasing as a result of the continuous growth of the lifetime and in consequence of the aging of the population. Many of these patients are treated with anticoagulants drugs to prevent arterial or venous thrombosis and in the same time they may need a dental procedure. Management of dental surgical procedures in these patients raises various issues between general dentists who have to balance between the bleeding risk and the thromboembolic risk. There are still differences in the approaches of general dentists and oral surgeons, some of them proposing temporary withdraw or reduction of anticoagulant doses, others suggesting the replacement of oral anticoagulants with low molecular weight heparins, fewer procedures being performed without changing in the therapy.

Until recently the only oral anticoagulants were vitamin K antagonists such as warfaine and acenocoumarol. At present new anticoagulants with a different mechanism of action and pharmacokinetics are available. They do not impose coagulating monitoring test, expose to a less important bleeding risk and have fewer drug interactions therefore becoming more and more used replacing warfain in community and hospitals. Because those drugs are relatively new, many dentists remain unfamiliar with their use. In order do proceed safe surgical interventions the doctors routinely interrupt the anticoagulant therapy no mater the dental procedure and so they may expose the patient to an increased thrombotic risk.

OBJECTIVE

The purpose of this paper is to review the new oral anticoagulants, to evaluate the impact of anticoagulant medications on dental treatment and to offer suggestions for the dental procedure management in patients taking those drugs.

MATERIALS AND METHODS

The primarily literature was consulted from product monographs and the medical literature in the electronic database through PubMed and Medscape using the following search terms: dabigatran, rivaroxaban, apixaban, dental procedures, oral bleeding. From the references of the articles obtained we selected additional references. We focused on selected articles evaluating the management of dental procedures in patients undergoing oral anticoagulant therapy.

RESULTS

The indications for anticoagulation are: myocardial infarction complicated with aneurism or intramural thrombus, prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or prosthetic replacement of cardiac valves, prophylaxis and treatment of venous and pulmonary embolism including prevention of postoperative venous embolism after orthopedic surgical procedures (hip fracture and prosthetic total hip or knee joint replacement).

Warfain and acenocoumarol are coumarinic anticoagulants preventing the reduction of vitamin K into active forms. They have the inconvenience that they demand anticoagulation monitoring by measuring the INR witch have different request therapeutic ranges depending on the disease: 2 to 3 for venous thromboembolism, stroke and atrial fibrillation, 2.5 to 3.5 for patients with prosthetic valves. The incidence and outcome of the bleeding is influenced not only by the dose reflected in the tall of INR but also by the age (anticoagulant effect increased with age), the presence of comorbid medical conditions, multiple current drugs, hypertension, renal or hepatic failure. Additional, there are food, drugs and herbal interactions.

The new oral anticoagulant agents have many properties different from warfain that make them safer and therefore preferred. They are indicated for thromboprophylaxis for adult patients undergoing elective hip or knee replacement surgery and stroke prevention for patients with nonvalvular atrial fibrillation. They are direct anticoagulants that target a single clotting factor inhibiting thrombin generation or thrombin activity: dabigatran is an oral thrombin inhibitor, while rivaroxaban and apixaban, are oral factor Xa inhibitors. Unlike warfain they have more predictable pharmacokinetics and pharmacodynamics so they proved similar or better anticoagulant effects but with lower rate of major hemorrhage. The onset of anticoagulation is rapid and they realize a stable anticoagulation at fixed doses. Therefore they do not need monitoring tests becoming an attractive anticoagulant alternative. Although current coagulation monitoring is usually not required, in special circumstances activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) for dabigatran and an anti–factor Xa assay for rivaroxaban may be used. In addition they have fewer interactions with other drugs mentioned in table 1 and they do not interfere with herbs so that may be used safely in patients using herbal medication. The new anticoagulants do not have food interaction or genetic polymorphisms that may alter drug metabolism. Although there is no specific antidote available for any of the new oral anticoagulants (however an antibody for dabigatran is under investigation) those drugs have a considerably shorter half lives than warfain (12-14 hours for dabigatran), so drug discontinuation will be sufficient for stopping the bleeding in most of the cases.

The new oral anticoagulants have similar onset of action and half life but they differ in their pharmacology and pharmakinetics having different mechanism of action, bioavailability and metabolism. Dabigatran is a direct selective and

reversible thrombin inhibitor, while Rivaroxaban and Apixaban are selective direct factor Xa inhibitors. Apixaban has low renal elimination so it is preferred in elderly patients and those with decrease renal function. Dabigatran and Rivoraxaban have dominant renal elimination and should not be

administrated in patients with creatinine clearance less than 30 ml/hour. A comparison of the new oral anticoagulants and warfain is summarized in table 1.

Table 1. Pharmacologic properties of oral anticoagulants

Properties	Rivaroxaban	Apixaban	Dabigatran
Target	Xa	Xa	IIa
Typical dosing schedule	Daily	Twice Daily	Twice Daily
Bioavailability (%)	80	50	6
Time to peak plasma concentration Tmax (h)	3	3	2
Half life (h)	7-11	9-14	12-17
Clearance (%)	66% renal 33% feces	25 % renal 56% feces	80 % renal
Increase of at least 50% in anticoagulant plasma concentrations	Clarithromycin Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole fluconasol	Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole	Amiodarone Dronedarone Ketoconazole Quinidine Ticagrelor Verapamil possibly macrolides
Decrease of at least 50% in anticoagulant plasma concentrations	Carbamazepine Phenobarbital Phenytoin Rifampin	Carbamazepine Phenobarbital Phenytoin Rifampin	Carbamazepine Rifampin Dexamethasone

The management of dental procedures in patients undergoing oral anticoagulation must be individualized on the type of procedure, bleeding and thrombotic risk. Damaging the gums and their highly vascular supporting structures may cause distressing bleeding some times life threatening, therefore many dentists discontinuous these drugs before any dental procedure. On the other hand current literature on warfain (Wahl, Devani et all) report that for many primary care dental procedures (single tooth extraction or minimally invasive procedure) there is no risk of significant bleeding in patients with INR therapeutical ranges and up to 3,5. [1, 2]. In addition the patients who stopped anticoagulants for dental procedures had an increased risk of embolic complications (by stopping medication but also by rebound effect) with fatal consequences in some cases. Many authors consider that the embolic risk outweighs the oral hemorrhagic risk, depending on the reason of anticoagulation. This hypercoagulability is due to increased thrombin production or platelet activation if therapy is abruptly discontinued. The risk of embolic complications is small but because it can be fatal most guidelines currently indicate that minor oral surgery in patients taking warfain with INR less than 3.5 may be done without adjustment in anticoagulation doses. The INR should be checked in the morning of the surgery in patient taking antivitamin K anticoagulants, some studies (Sanz et al.) concluding that most of these patients do not have INR within the therapeutical range

when attending a dental practice probably because of the food and drug interactions [3]. In procedures where moderate or significant bleeding is expected the dentist should consult the patient's physician who should manage the adjustment of antivitamin K doses until INR achieve less than 3.5 - 3, but the expected value as a reflection of reducing doses will not be reached earlier than in 3 or 4 days. Some authors recommend that in patients with high thromboembolic risk undergoing to a high risk dental procedure(e.g. generalized subgingival cleaning or gingival surgery, simple multiple extraction- more than 5 teeth, more than one implant, soft tissue biopsy larger than 2,5 cm or osseous biopsy, surgical

extractions, jaw surgery or resection of head and neck tumor) vitamin K antagonist will be replaced with low molecular weight heparins before the surgery and in the morning of the procedure the last one will be withhold [4].

Recent studies have shown that the bleeding profile of the new oral anticoagulants, in particular of life-threatening bleeding (e.g. intracranial hemorrhage) is more favorable than that of warfarin. Due to lack of data in the literature there are currently no definitive dental management recommendations for patients on the new oral anticoagulants, and the recommendations on bleeding management are not so much based on clinical experience, but rather reflect experts' opinions or laboratory endpoints. RELY trial had evaluated bleeding risk and founded no significant difference between the patients on warfain and those on dabigatran. Common interventions with no clinically important bleeding risk can be performed at trough concentration of the NOAC. (i.e. 12 or 24 h after the last intake, depending on twice or once daily dosing). Because of its short duration of action, drug withdrawal and local haemostatic measures are likely sufficient in most of dental procedures without the need of discontinuing the drug. However, in patients with comorbidities or in high risk dental procedures where significant bleeding is expected, the new oral anticoagulants may be discontinued 12-24 hours pre-operatively (and restarted 24 hours post-operatively), in consultation with the patient's physician (table 2).

	VITAMIN K ANTAGONIST	**NEW ANTICOAGULANTS**
LOW RISK PROCEDURES	No change	No change
MEDIUM RISK PROCEDURES	For INR ≤ 3,5 No change Local hemostatic measures	No change Local hemostatic measures
HIGH RISK PROCEDURES	For INR ≤ 3 no change For INR > 3 consider - Low risk for thromboembolism: Withdraw drug or reduce dose to allow INR to fall - High risk for thromboembolism: Withhold warfarin, convert to LMWH. Withhold LMWH on the morning of the procedure	Withhold 24 hours prior to procedure Local hemostatic measures Restart after hemostasis is achieved

Table 2. Risk of procedure and anticoagulant management

Some authors suggest that even in low or medium risk procedures it may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 hours later, skipping one dose for oral anticoagulants normally administrated twice a day [5].

For dabigatran, a more graded pre-intervention termination depending on kidney function has been proposed in high-risk interventions (stopping the drug 2 to 3 days before), although many of these patients may be on the lower dose (110mg twice a day instead of 150 mg).

Co morbid diseases as liver diseases, renal diseases, bone marrow disorders, leukaemia increase the risk of oral bleeding. Inflammation of oral tissues increase the risk of bleeding therefore these patients should be referred o a maxillofacial surgery clinic.

Certain drugs used by the dentist for pain control, anesthesia or infection can interfere with the anticoagulant action.

The association with platelet aggregation inhibitors (aspirin, clopidogrel, ticlopidine) and nonsteroidal anti-inflammatory drugs additional increase the risk of bleeding in patients under both warfain and new anticoagulants. Therefore aspirin or nonsteroidal anti-inflammatory drugs should not be used for pain control after dental procedures in these patients.

Aceminophen and COX 2 specific inhibitors may be used in reduced doses for postoperative pain control. Opioid analgesic increase the action of rivoroxaban so should be used with caution.

In patients taking oral anticoagulants block anesthetic techniques are not recommended. Inferior alveolar nerve block are accepted in patients taking warfain and having INR under 3. For local anesthesia intraligamentary and intraseptal techniques produce less bleeding complication therefore they are safer.

For patients undergoing vitamin K antagonists we have to keep in mind that some antibiotics induce reduction in prothrombin activity or intestinal flora essential for vitamin K production: macrolide antibiotics (erythromycin, clarithromycin and possible azitromycin), sulphonamides, treacycline and doxyciline, the second and third generation cephalosporines, levoflocacin, metronidazole. Other drugs like the barbiturates, carbamazapin, thazidede diuretics may antagonize the effect of warfain.

The new oral anticoagulants are reported to have few drug interaction. Rivaroxaban must not be associated with systemic azoleantimycotics (only fluconazol have a less interaction), macrolide antibiotics (especially erythromycin and clarithromycin), opioid analgesics and HIV protease inhibitors (ritonavir).

The dental procedures in patients under oral anticoagulants should be done with minimal trauma and local measures for control a postoperative hemorrhage must be used: local pressure, absorbable gelatin compressed sponges, topical thrombin powder, gelatin sponges with thrombin solution (that must not be used with oxidized cellulose or microfibrilar collagen because they inactivate the thrombin), oxidized cellulose or microfibrilar collagen hemostat, tranexamic acid mostly in an oral rinse 4 times a day for 2 days (or rarely tablets or iv injections), additional suturing, electrocauterization. Fibrin sealants (or fibrin glues) are derived mainly from blood plasma and contain two components that interact during application and mimic the final steps of the blood coagulation cascade, forming a stable fibrin clot. They can be applied to very small blood vessels and to areas that are difficult to reach with conventional sutures and they control the bleeding by speeding up the formation of a stable clot. In addition, they reduce the risk of postoperative inflammation or infection and they are absorbed by the body during the healing process. Therefore the fibrin sealants are particularly useful for minimally invasive procedures and for treating patients taking anticoagulants.

In addition, in cases with multiple extractions, Little et all recommends to construct a splint before surgery to cover the surgical area, which will protect the clot. Tthe sponges with thrombin can be packed

beneath the splint. Also, primary closure over the sockets is desirable. [6].

Most of the dental postoperative bleedings are minor and not life-threatening and local haemostatic measures can control it, especially in patients undergoing new oral anticoagulants. However if the bleeding is aggressive, in patients taking warfain or acenocoumarol the administration of vitamin K may be useful although it has a slow onset (i.e. at least 24 h). Occasionally fresh frozen plasma or coagulation factors can be use to restores coagulation. There is no specific reversal agent or antidote for the new oral anticoagulants but their short half-life means that the discontinuation of the drug is likely to be sufficient to correct most bleeding problems. Strategies for the reversal of the anticoagulant effects are limited, and the plasma abundance of the drug may block newly administered coagulation factors as well. In cases of severe bleeding may be considered: fluid replacement, transfusion or blood product, even restricted and expensive blood products - recombinant activated factor VII, prothrombin complex concentrate (only for anti Xa inhibitors) or hemodialysis for dabigatran.

CONCLUSIONS

Dental management recommendations for patients on the new oral anticoagulants, and the recommendations on bleeding management are not currently definitive in the literature and they are not so much based on clinical experience, but rather reflect experts' opinions or laboratory endpoints. Recent studies have shown that the bleeding profile of the new oral anticoagulants is more favorable than of warfarin because of their predictable and stable anticoagulant effects and lower risk of drug interaction, so that dental management may be safer and easier with these drugs. Most authors agree that the thromboembolic risk due to withdrawal of oral anticoagulants outweigh the risk of bleeding and therefore they recommends in most of the cases that dental procedures may be allowed without discontinuing doses. In patients with comorbidities or in high risk dental procedures where significant bleeding is expected, the new oral anticoagulants may be discontinued 12-24 hours pre-operatively (and restarted 24 hours post-operatively), in consultation with the patient's physician. However, the final decision will depend on each patient, surgeon and the surgery bleeding risk.

In patients undergoing new oral anticoagulants most of the dental postoperative bleedings are minor and not life-threatening can be controlled with local haemostatic measures: absorbable gelatin compressed sponges, gelatin sponges with thrombin solution oxidized cellulose or microfibrilar collagen hemostat, tranexamic acid.

It is strongly recommended to obtain medical consultation before the dental procedure, to evaluate comorbidities and co medication. Special attention appears to be needed to assure the safety of the concomitant use of nonsteroidal anti-inflammatory drugs and opioid analgesics that may prolong bleeding with some of these new anticoagulants. In patients taking antivitamin K, INR value must be requested in the morning of the dental procedure.

Other practical advice for anticoagulated dental patients may be to schedule the dental procedures early in the day and early in the week to allow more time to deal with bleeding if it occurs. If anticoagulation is only temporary (e.g. venous thromboembolism prophylaxis post-hip or knee replacement) and the dental procedure is not an emergency, consider postponing elective dental procedures until anticoagulation is no longer needed.

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