 DOI: 10.1515/acm-2017-0008

DIRECT ORAL ANTICOAGULANT DRUGS IN DENTAL CLINICAL PRACTICE

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Abstract

The direct oral anticoagulant drugs (DOAC) are generally safe and effective in several clinical settings including acute venous thromboembolic disease, prophylaxis in the postoperative setting, prevention of thromboembolism in patients with non-valvular atrial fibrillation, and in the management of acute coronary syndrome. The relatively short half-life, rapid onset of action, and predictable pharmacokinetics should simplify periprocedural use of the DOAC. The aim of this work is to propose and summarize periprocedural management of patients treated with the DOAC in dental practice and to inform about the principal specifications of this treatment.

Key words: dental practice, direct oral anticoagulant drugs, laboratory monitoring, periprocedural management, risk of bleeding.

INTRODUCTION

Dentists, in clinical practice, come into contact with a wide range of patients requiring basic invasive procedures. Due to the aging population with multiple comorbidities, the dentists are more frequently facing invasive dental procedures in patients with anticoagulants.

Recently, a new option for anticoagulant treatment with progressive characteristics has emerged. The aim of this work is to design an approach to the periprocedural dental management of patients treated with the direct oral anticoagulants (DOAC, formerly known as NOAC- new oral anticoagulants or TSOACs- target-specific oral anticoagulants), as well as to inform about the principal specifications of this treatment.

The traditional oral anticoagulant drugs like vitamin K antagonists (VKA- especially warfarin), commonly used in the management of thrombosis, have got many drawbacks (1,2).

A narrow therapeutic window and need for laboratory monitoring are the main disadvantages of VKA. The DOAC (Table 1), dabigatran, rivaroxaban, apixaban and edoxaban (the last one recently launched in Slovakia), which have been gradually introduced and implemented for clinical practice over the years since 2008, eliminate the drawbacks of conventional anticoagulants (Table 2) (3,4,5,6).

Due to the efficacy, safety and predictability of the pharmacokinetics of the DOAC, as it was confirmed in large clinical trials (RE-LY, RE-MEDY, RE-COVER, RE-SONATE, RECORD, EINSTEIN, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48, etc.), the DOAC with standard doses do not require routine monitoring (according to the Summary of Product Characteristics (SPC) of these drugs) (7,8,9). The relatively short half-life, rapid onset of the action and predictable pharmacodynamics can simplify the perioperative management of

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the DOAC. However, there are certain specific situations including the preparation for urgent invasive procedures, when laboratory investigation of DOAC´s concentration is necessary.

Tab. 1 DOAC characteristics (10,11 – modified by Stasko J. et al.)

characteristics	dabigatran	rivaroxaban	apixaban	edoxaban
prodrug	yes	no	no	no
target	FIIa (thrombin)	FXa	FXa	FXa
bioavailability	≤ 6,5 %	~ 90 %	~ 50 %	62 %
P-glp interaction	yes	yes	yes	yes
time to peak	1–2 h.	2–4 h.	1–2 h.	1–2 h.
biological half-life	12–17 h.	5–13 h.	8–15 h.	10–14 h.
plasma protein binding	33 %	90 %	87 %	55 %
dosage	bid	od	bid	od
liver clearance	↓↓	33 % (CYP 3A4, 2J2)	75 % (CYP 3A4)	50 % biliary/intestinal
kidney clearance	≤ 80 %	33 %	25 %	50 %
specific antidote	yes	no	no	no

P-glp, P-glycoprotein; max., maximal; CYP 3A4, 2J2, cytochrome P450; od, once daily; bid, twice a day

Advantages and disadvantages of DOAC

The oral administration, simple mechanism of action (independent from antithrombin), predictable pharmacokinetics and few interactions with other drugs compared to the VKA are to be the greatest advantages of the DOAC (Table 2) (7,8,9). Up to now, absence of the "specific" antidote for DOAC had been considered as the main disadvantage of DOAC. In the present time this shortage is eliminated throught the recently marketed first antidote for dabigatran, namely, idarucizumab (fully humanized Fab antibody fragment), which is available for clinical practice in Slovak hospitals since 03/2016. Specific xaban´s antidote, inactive analog of FXa - andexanet alpha, selectively inhibiting both direct and indirect FXa inhibitors, is expected to be available soon. The potentially inadequate increase of DOAC´s plasma concentration in patiens with renal insufficiency is an important disadvantage of these drugs. Therefore, the dabigatran use is contraindicated in glomerular filtration rate (GFR) <30 ml / min. and xabans should not be recommended in GFR <15 ml/min. (Table 2) (7,8,9). Nevertheless, the mentioned benefits of DOAC overbalance their drawbacks and present increased comfort for both, the patient and physician.

DOAC and preoperative management for elective surgery

Urgency of the procedure, half time of DOAC, the risk of bleeding associated with the surgical procedure and the risk of thrombosis due to DOAC discontinuation should be considered before performing surgical procedure. Timing for preoperative and postoperative discontinuation of DOAC is crucial to ensure minimal (DOAC concentration 3–6 % when performing surgery with high risk of bleeding and concentration 12–25 % when performing surgery with low risk of bleeding, respectively) or no residual effect of DOAC at the time of surgery.

Tab. 2 DOAC advantages and disadvantages (7,8,9 - modified by Stasko J. et al.)

advantages	disadvantages
oral application form	unavailable direct antidote (except of dabigatran)
predictable pharmacokinetics	accummulation in renal insufficiency: – dabigatran is CI in ClCr <30 ml/min. – apixaban, edoxaban and rivaroxaban are not recommended in ClCr <15 ml/min.
simple mechanism of action (antithrombin independent)	

CI, contraindicated; ClCr, creatinine clearance

It must be taken into account: a) elimination half-life of DOAC; b) the patient's renal function, and 3) the type of the elective surgical procedure and anesthesia (12).

Dabigatran

Half-life of dabigatran and preoperative discontinuation of dabigatran is to the greatest extent dependent on renal clearance of dabigatran (> 80 %). The dabigatran has got a half-life of 12–17 hours in patients with normal (GFR> 80 ml / min.) or slightly reduced renal function (GFR, 50–80 ml / min.) (10,11). Therefore, the final dose of dabigatran in patients with high risk of bleeding should be stopped 2–3 days before the surgical procedure and one to two days before the surgical procedure in patients with normal risk of bleeding (Table 3). (7) Patients with a moderate decrease in renal function (GFR 30–50 ml/min.) have a half-life of dabigatran 16–18 hours. According to the SPC in patients with moderate decrease in renal function (GFR 30–50 ml / min.) the last dose of dabigatran should be administered four days before the surgical procedure with high risk of bleeding or 2–3 days prior to surgery with the standard bleeding risk (Table 3) (13).

Tab. 3 Dabigatran- preoperative management and elective surgery (13 - modified by Stasko J. et al.)

renal function (ClCr)	biological half-life (hours)	interruption of treatment before surgery	
		high risk of bleeding (4–5 half-lives)	common risk of bleeding (2–3 half-lives)
≥ 80 ml/min	12–17	2 days	1 day
50–80 ml/min	14–17	2–3 days	1–2 days
30–50 ml/min	18–24	4 days	2–3 days
< 30 ml/min*	> 24*	> 5 days*	2–5 days*

Note* according to SPC dabigatran administration is contraindicated in ClCr < 30 ml/min

Apixaban, edoxaban and rivaroxaban

Preoperative discontinuation of apixaban, edoxaban and rivaroxaban depends on: 1) the half-life of the drug (apixaban 8–15 hours, edoxaban 10–14 hours and rivaroxaban 5–13 hours) and 2) the renal clearance of the drug (apixaban 25 %, edoxaban 50 % and rivaroxaban 33 %) (10,11,14). According to SPC the administration of edoxaban and rivaroxaban should be discontinued at least 24 hours prior to the procedure, and treatment should be restarted as soon as the clinical situation allows (8). Discontinuation of edoxaban and rivaroxaban 48 hours

prior to the procedure is recommended in case of performing surgery with high risk of bleeding (Table 4) (12,15).

According to SPC the apixaban should be discontinued 48 hours before surgery with moderate to high risk of bleeding. When performing a low risk of bleeding procedure, the treatment with apixaban should be discontinued 24 hours prior to the surgery (Table 4) (15). Apixaban therapy should be resumed as soon as the clinical situation permits. In patients with severe reduction in kidney function (GFR, 15–30 ml/min.) discontinuation of apixaban, edoxaban and rivaroxaban is recommended four days prior to the surgery with high risk of bleeding or two days before surgery with normal bleeding risk (Table 4) (15).

Tab. 4 Apixaban, edoxaban and rivaroxaban preoperative management and elective surgery (15 - modified by Stasko J. et al.)

anticoagulant	renal function (ClCr)	interruption of treatment before surgery	
* APIXABAN, EDOXABAN, RIVAROXABAN		high risk of bleeding (4–5 half-lives)	common risk of bleeding (2–3 half-lives)
	> 30 ml/min.	2 days	1 day
	15-29.9 ml/min	4 days	2 days

Note* according to SPC apixaban, edoxaban and rivaroxaban administration is not recommended in ClCr < 15ml/min

Perioperative management principles of dental patients with DOAC treatment

Thorough medical history of the patient, the type of antithrombotic therapy and other drugs potentially increasing bleeding risk need to be checked before invasive dental treatment. Prerequisites for successful invasive procedure also include adequate material equipment and sufficient erudition of the health personnel.

Most of the dental procedures belongs to the category of procedures with very low or low risk of bleeding. Of course, the risk of perioperative bleeding, especially in a case of major surgical procedure will increase depending on the actual DOAC plasma concentration (Table 5).

In this situation, as well as in patients with impaired kidney function prepared to the dental procedure with even low or moderate risk of bleeding the consultation with doctor indicating anticoagulant treatment (usually an internist or cardiologist) and consultation with a hematologist is recommended to consider monitoring of DOAC.

Do patients with DOAC continue treatment perioperatively in these procedures?

Therefore, even in patients treated with DOAC perioperative discontinuation of treatment is not necessary when performing dental procedures such as tooth extraction, or extraction up to 3 teeth not more than in two quadrants, as the risk of bleeding is significantly lower using the DOAC than VKA (16). In such an approach, the levels of routine coagulation tests (aPTT, TT, PT) at the time of dental procedure are assumed to be normal or only slightly prolonged. Therefore, in these procedures the laboratory monitoring of DOAC with special quantitative tests is not recommended. Exceptionally, even when performing procedures with a very low risk of bleeding (i.e. the single tooth extractions), DOAC monitoring may be necessary in patients with impaired kidney function or in case of possible drug interactions (e.g. concentration of DOAC is decreased by rifampin, carbamazepine, phenytoin; concentration of DOAC is increased especially by ketoconazole, dronedarone, cyclosporine and in less extent by verapamil, amiodarone, quinidine, clarithromycin, ticagrelor, etc.) (11). In these situations the consultation with hematologist and specialist indicating anticoagulant treatment is necessary. If a mild reduction of the GFR (> 50 ml / min.) is found, there is recommended in the high risk of thrombosis to post-

Tab. 5 Anticoagulant treatment and risk stratification in dentistry (16 - modified by Stasko J. et al.)

dental procedure	lower than therapeutic levels of DOAC/levels prior to administration of next dose	therapeutic levels of DOAC
supragingival tooth filling sugingival scaling and root planing simple topical anesthesia	presumed low risk of bleeding	presumed low risk of bleeding
subgingival filling simple endodontic treatment simple tooth extraction regional anesthesia	presumed low risk of bleeding	presumed higher risk of bleeding
dentoalveolar surgery (bone preparation) multiple teeth extractions	presumed higher risk of bleeding	presumed higher risk of bleeding

Preparing of surgical procedures with very low risk of bleeding, such as simple tooth extraction or extraction up to three teeth in patients treated with DOAC is similar to those treated with VKA.

pone the morning dose of DOAC up to 4 hours after the procedure. In contrast, in patients with a low risk of thrombosis (CHADS2 ≤ 2, provoked thrombosis> 6 weeks) and the same reduction of GFR we interrupt DOAC treatment 24 hours prior to the procedure, similarly to the procedure with low risk of bleeding. In moderate and severe reduction in GFR (<50 ml/min.) we interrupt DOAC treatment 48 hours prior to the procedure (especially in dabigatran), similarly as for the procedure with low risk of bleeding (Table 3 and Table 4).

Generally, in most patients with anticoagulant therapy (patients on low molecular weight heparin - LMWH, patients on VKA with INR in the therapeutic range 2.0–3.0 or DOAC patients with standard dosage and no kidney function deterioration neither severe hepatic insufficiency) it is possible to perform routine dental surgery without major risk of bleeding with no preoperative precautions (17). Laboratory monitoring of routine coagulation tests (aPTT, TT, PT) is not necessary before dental surgery in the absence of impaired kidney function and severe hepatic insufficiency in patients treated with DOAC. In contrast, the knowledge of INR value preoperatively is important in patients treated with VKA (warfarin) due to frequent "fluctuation" of INR levels. The risk of bleeding in standard DOAC treatment is expected to be comparable with risk of bleeding found in the patients on VKA within therapeutic INR range (INR 2.0-3.0) or more often – hemorrhage is present with lower intensity than in the VKA (17). Some authors distinguish the high risk of bleeding in case of performing longer and major risk procedure > 45 min. (oncological surgery) and low bleeding risk < 45 min. (normal teeth extractions) (18,19). Bleeding risk estimation based on this relationship in association with dental treatment procedures is shown in table. (Table 5) Prior to extensive dental procedures or upon the occurrence of other bleeding risk factors it is necessary to cooperate with the doctor prescribing antithrombotic therapy (especially with hematologist) and to prepare patient in special oral surgery department. (17) Such situations may require preoperative measures even temporary discontinuation of DOAC treatment could be necessary (see tables with preoperational DOAC dosing, Table 3 and 4).

Other measures in the management of dental patients treated with DOAC

The prefered time for management of the elective surgical procedure should be a begining of the week in the morning. The procedure should be performed with caution and consideration.

Concerning dental procedures in patients with DOAC the importance is generally placed particularly on local measures. (14). Immediately after the procedure it is recommended to treat the wound thoroughly, i.e. to perform suturing of the postextaction wound including use of local hemostyptic agents (based on collagen, oxycellulose, thrombin or fibrin tissue adhesives and others). Rinsing the wound with tranexamic acid is optional. Local treatment can be completed with intravenous injection of etamsylate (1–2 ampoules). Intramuscular etamsylate administation should be avoided due to the risk of hematoma formation in DOAC patients! It is necessary to instruct the patient about the post-operative mode both orally and in writing. The patient should avoid rinsing his mouth, spitting, sucking actions, drinking beverages through straws, smoking, drinking hot liquids for at least 24 hours after procedure and eating or drinking for at least three hours after the procedure (until clot is stabilized and the effect of local anesthetics is not fully cancelled). The patient should also apply ice (in a wrapped cloth) on the area of preparation to reduce bleeding risk, as well as to ease the swelling and pain. It is also possible to administer analgesics - but only those which do not affect platelet function (drugs based on paracetamol or metamizole). Do not administer analgesics with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (based on ibuprofen, diclofenac, naproxifen etc.). The patient should be provided with dressing materials, which could be used in case of bleeding for local compression of the wound. Patients should be informed about bleeding risk as well as dental emergency and oral surgery department contacts (20,21,22).

CONCLUSION

The vast majority of patients treated with DOAC has no increased risk of bleeding in a wide range of routine dental surgical procedures. Conversely, risk of thromboembolism (potentially life threatening) has been proven more dangerous for patient when discontinuing DOAC treatment.

Based on the available literature data for the vast majority of dental treatment (high or low risk of bleeding) it is recommended not to discontinue DOAC treatment prior to the procedure. However, the risk of bleeding resulting from the nature of procedure, as well as the patient's characteristics such as co-morbidities and other factors (in particular the reduction in renal function or severe hepatic insufficiency) should be carefully considered preoperatively (especially in large maxillofacial surgery, multiple dental extractions, etc.). All surgical procedures should be completed as atraumatically as possible with following thorough local wound treatment. In addition, in patients with high risk of thromboembolism and elective procedures with a high risk of bleeding, surgery should be supported by consultation with doctor indicating anticoagulant therapy (usually internist or cardiologist), hematologist (preoperative measures, possibly laboratory monitoring) and most importantly with oral surgeon.

List of abbreviations

aPTT – activated partial thromboplastin time
bid – twice (two times) a day
DOAC – direct oral anticoagulant drugs
Fab – fragment antigen binding
GFR – glomerular filtration rate
CHADS2 – score used for risk stratification of ischemic stroke in patients with non-valvular atrial fibrillation
INR – international normalized ratio
LMWH – low-molecular-weight heparin
NOAC – new oral anticoagulants
od – once a day
PT – prothrombin time

SPC – summary of product characteristics
TSOACs – target-specific oral anticoagulants
TT – thrombin time
UFH – unfractionated heparin
VKA – vitamin K antagonists

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Received: March, 9, 2017
Accepted: May, 13, 2017