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Clinical Guidelines for the General Practitioner in Patients Taking Direct Oral Anticoagulants (Doacs)

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Abstract

Purpose: To suggest clinical guidelines for the general practitioners or the oral surgeon in patients prescribed with Direct Oral Anticoagulant (DOACs).

Methods: An electronic search was made in the databases PubMed (MEDLINE), limited to articles in english or spanish in the last ten years.

Results and discussion: The studies reviewed recommend to analyzed the patient individually by its bleeding and thromboembolic risk. Further more, the kidney fuction and the dental procedure should be taken into account. Low or medium risk patients with a normal renal function do not have to postpone or dismiss a dose. Local haemostatic measures must be guaranteed in any procedure.

Clinical significance: It is very important, even vital, the knowledge and management of Oral Direct Anticoagulants in order to prevent haemorrage when performing any dental treatment. SARS-CoV-2 infection could increase the number of patients taking these drugs.

Introduction

Life expectancy with its consecuent age-increasing of the population has become a challenge in the past years both for the general dentist and the oral surgeon, because of the tough situations of the polimedicated patients, concomitant diseases and the need of oral care. A survey from UK revealed that 80% of the patients over 65 years are partial edentulous. This situation force the oral surgeon to provide several treatments in order to improve its health and life quality [1].

There are some important complications that can occur during our treatment in health-compromised patients such as osteonecrosis associated with bisphosphonate or the possibility of suffering an hemorrhage, among others [1].

It is known that cardiovascular diseases increase the morbidity and mortality worldwide. These patients need drugs to combat thromboembolisms, as antiaggregants and anticoagulants, which play such an important role in the disease [1].

Within chronic heart arrhythmias, auricular fibrilation is the most frecuent disease. The treatment is not only the heart frecuency monitoring but also the antithrombotic treatment [2].

Since aproximately 60 years ago, vitamin K antagonists (VKA) as Warfarin, have been using for the prevention and treatment of different entities that course with risk of thromboembolic accident. Due to its limitations, in the last decade new oral anticoagulants have been developed, which nowadays are known as Direct Oral Anticoagulants (DOACs) [2].

There are 4 drugs which belong to this group: Dabigatran (Pradaxa®, Boehringer Ingelheim International GmbH, Germany), Rivaroxaban (Xarelto®, Bayer AG, Germany), Apixaban (Eliquis®, Bristol-Myers Squibb/Pfizer EEIG, Ireland) y Edoxaban (Lixiana®, Daiichi Sankyo Europe GmbH, Germany). These drugs were developed with a huge terapeutic variety, fixed doses with no need of monitoring, and few interactions [3].

The main difference between the classical and the new drugs is the mechanism of action: The VKAs act probing a reduction in the synthesis of II, VII, IX and X factors, dependants of vitamin K. Nevertheless, DOACs inhibit directly specific zones of coagulation cascade either thrombin (Dabigatran) or factor Xa (Rivaroxaban, Apixaban, Edoxaban) [2-5].

Several published studies, like RE-LY, ROCKET-AF, ARISTOTLE, or ENGAGE AF-TIMI 48, have shown that DOACs are equal or superior than VKAs in terms of prevention of ischemic heart disease or hemorrhage, without monitoring [3,6].

The world pandemic crisis by the SARS-CoV-2 infection has become a challenge for the medical community. It has been demostrated that SARS-CoV-2 modified the production, condition and dysfuntion of the platelets that could lead to several coagulation disorders such as venous thromboembolsm or other medical conditions as ischemic cardiopathy, diabetes, lung or liver disorders, etc. [7-9].

This epidemiological situation could lead the medical community to think that these drugs will be prescribed worldwide causing a new challenge in different medicine specialities.

The aim of this article is to suggest clinical guidelines for the general practitioners and oral surgeons for their daily practice in the prevention and treatment of the patient with DOACs.

Material and Method

A digital search was carried out in the electronic databases of PUBMED-MEDLINE, with the follow search strategy: ((((“mouth”[MeSH Terms] OR “mouth”[All Fields] OR “oral”[All Fields]) AND direct[All Fields] AND (“anticoagulants”[All Fields] OR “anticoagulants”[MeSH Terms] OR “anticoagulants”[All Fields] OR “anticoagulant”[All Fields])) AND (“surgery, oral”[MeSH Terms] OR (“surgery”[All Fields] AND “oral”[All Fields]) OR “oral surgery”[All Fields] OR (“oral”[All Fields] AND “surgery”[All Fields]) OR “oral surgery”[All Fields] OR “oral surgical procedures”[MeSH Terms] OR (“oral”[All Fields] AND “surgical”[All Fields] AND “procedures”[All Fields]) OR “oral surgical procedures”[All Fields] OR (“oral”[All Fields] AND “surgery”[All Fields]))) AND extraction[All Fields]) AND (“tooth”[MeSH Terms] OR “tooth”[All Fields] OR “teeth”[All Fields]).

It was limited to the last ten years, including randomized clinical trials, systematic review, case series or case report published in English or Spanish. Opinion articles, *in vitro* trials and animal trials, were discarded.

Results and Discussion

Clasically, AVKs (Warfarin and Acenocoumarol) has been used for prevention and treatment of the thromboembolic disease. It is a serious medical condition associated with significant morbidity and mortality, and an incidence that is expected to double in the next forty years. Moreover, they present several inconvenient: The action beggining is slow, the requirements of monitorization (International Normalized Ratio: INR) and dose check. In the past few years, DOACs have shown a positive benefit-risk ratio with prevention of both ictus and thromboembolism Disease [10].

On the one hand, one of the first differences with classic AVKis that monitorization is not needed with DOACs. Indeed, classic values for controlling anticoagulant status as INR or APTT do not reproduce the anticoagulant degree precisely in DOACs and the different laboratory exams are not easily accesible [6].

Regarding adverse effects, pharmacological interactions are described with DOACs that might either enhance or inhibit the anticoagulation status, as happen with AINES, some antibiotics (clarythromicin, clorhanphenicol), corticosteroids (dexamethason), benzodiazepins (carbamazepin) or antiepileptics (fenobarbital) [6,11].

Classically, with AVks, the recommendation was to suspend the Warfarin five days before the surgery, replacing with Low Molecular Weight Heparin (LMWH). The aim was to reduce the bleeding risk without compromising the thromboembolic situation. Even though the management of these drugs is well documented in the literature, it management is different with the DOACs [5].

Generally, the postoperative bleeding risk after dental extractions and osteotomies in patients with DOACs treatment is low, and easily controlable with local haemostatic measures, so it is recommended not to discontinuate the DOACs treatment for dental intervention, avoiding the risk of a thromboembolic episode [12].

Despite the limitations of observational studies, evidence suggests that significant differences exist between DOACs, specially in terms of predisposition to bleeding, being Apixaban the one with more security profile [13].

The Brennan, et al. study compared the bleeding outcomes in two groups without discontinuating the drug dosification. One group was taking DOACs and the other group was receiving warfarine with a INR between 2.0 and 4.0. The results revealed a difference in the bleeding between the DOACs group (36%) versus the warfarine group (43%). Moreover, three different DOACs were used: apixaban, dabigatran and rivaroxaban. The study showed that rivaroxaban had the higher level in the bleeding amount. The authors suggest that there is

no need of adjust the dosification of the DOACs when a dental extraction is performed [14].

However, there are special situations that must be taken into account. Ehrhard, et al. described a patient with an impaired renal function that after a dental extraction suffered a severe en oral bleeding that requiered the suspenction of the DOACs and the use of LMWH to stop the bleeding [15]. So, the importance of a correct diagnosis, stablishing the bleeding risk and thromboembolic situation must be analized individually.

Nevertheless, despite the published data, up to this date, there are not any trials that compare DOACs between each other [3]. Furthermore, the principal issue these drugs had, has been resolved with the appearence of Andexanet alfa (Ondexxya®, Portola Netherlands B.V., The Netherlands), antidot for the factor Xa direct inhibitors, and Idarucizumab (Praxbind®, Boehringer Ingelheim International GmbH, Germany) for Dabigatran, both with abundant scientific support to defend their safety and efficacy [16-18].

How Should it be the Management in Patients Taking Doacs?

Literature does not present a strong consensus in terms of management of the patients with DOACs, not even between each country. Different protocols have been described by several doctors depending on the INR, on the procedure or the patient [3,19-21].

Systematic reviews by Bensi, et al. and Sáez-Alcaide, et al. reported higher bleeding rates in patiens taking DOACs versus healthy patients and described the importance of the local haemostatic measures or the need of further clinical studies [22,23].

On one hand, specific scales have been created in order to evaluate the thromboembolic risk (CHA2DS2-VASc) (Table 1) or the bleeding risk (HAS-BLED) (Table 2), classifiying the risk, as low, moderate and high. On the other hand, surgical procedure must be considered (Table 3) [6,23,24].

Regarding the thromboembolic risk, factors like age, gender, hypertension, diabetes or heart diseases

Table 1: Thromboembolism risk (CHA2DS2-VASc Score).

Legend	Risk factor	Points
C	Congestive heart failure/dysfunction	1
H	Hypertension	1
A2	Age (more than 75-years-old)	2
D	Diabetes mellitus	1
S2	Stroke/Thrombo-embolism	2
V	Vascular disease	1
A	Agebetween 65-74 year-old	1
Sc	Sex category (female gender)	1
Maximum score		**9**

Table 2: Bleeding risk (HAS- BLED Score).

Legend	Risk factor	Points
H	Hypertension	1
A	Abnormal liver or renal function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labil INR	1
E	Eldery (more tan 65-years-old)	1
D	Drugs or alcohol	1 or 2
Maximum score		**9**

Table 3: Procedure risk

Low	Simple extraction, biopsies < 1 cm, tartrectomies and restorative procedures
Moderate	Multiple extractions, > 1 cm biopsies, infragingival tartrectomies
High	Surgical extractions, big extensión biopsies, regenerative surgeries and extensive implants treatments

should be considered, whereas the age, INR, bleeding, renal disfunction or tobacco/drugs consumption must be considered as bleeding factors. These patients would have low risk with 1 or less points, moderate risk with 2 points, and high risk with 3 or more points [6].

Depending on the surgical procedure, low risk interventions are considered simple extractions, less than 1 cm biopsies, tartrectomies and restorative procedures. Moderate risk interventions are multiple extractions, more than 1 cm biopsies or infragingival tractrectomies. High risk interventions are those who implicate surgical extractions, big extension biopsies, regenerative surgeries or extensive implants surgeries [6,23,25].

The implant placement will depend on the surgical procedure and patient´s characteristics Implant surgery performed with minimal invasive or transmucosal methods, are considered as low risk interventions, whereas conventional and regenerative surgeries should be considered as high risk interventions.

Furthermore, we should minimize bleeding risk as much as posible, and different protocols recommend to carry out the procedures with vasoconstrictor anesthesia, as soon as medical condition of the patient allows it, avoiding ostectomy or agressive mucoperiosteal flap detachment, the use resorbable suture and haemostatic agents that stimulate the correct clot formation [6].

It is also important to evaluate the renal function before prescribing the DOAC. The anticoagulant effect depends on renal function. The maximum anticoagulant effect occurs two hours after the drug intake, and it progressively decreases with the time. With a decreased renal function, the elimination procedure increases, and the drug remains active during the time. This must be really considered at the time of performing a surgery on these patients [12,25,26].

Despite the recommendations, both general dentist and surgeon are obliged to ask for the informed consent to perform the procedure, clearly know the medication and posology, and take the neccessary measures to ensure the haemostasy and minimize the risk of developing a postoperative haemorrhage [3].

According to the studies reviewed, as long as the patient has a normal kidney fuction, with low-medium haemorrhage and thromboembolic risk, the drug administration should not be modified and local haemostatic measures should be guaranteed. In case of a high risk, the DOACs could be discontinuated for at least 24-hours, depending on the renal function [25].

Conclusions

It is very important to fullfil a correct clinical history, as well as know which DOAC is prescribed in each patient, and its posology. General dentists and oral surgeons must take care to ensure haemostasis and minimize the risk of having a postoperative haemorrhage. Low or médium risk, with a correct kidney fuction should continue the normal drug dosification.

In case of doubt, a refferal with the doctor in charge on the drug prescription should be done and be sure of having the specific informed consent.

Disclosure Statement

Authors do not have any conflict of interest. All authors of this manuscript certified that they had no propietary, financial or other interest in any product presented in this article.

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