Novel oral anticoagulants: a practical guide for dentists

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**KEYWORDS**
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**ABSTRACT**
The purpose of this work is to illustrate the features and usage of novel oral anticoagulants (NOACs) and clarify any adjustments to the dosage or its suspension based on surgical needs, with particular reference to dental procedures. In fact, the dental management of patients undergoing anticoagulant treatment with novel oral anticoagulants, NOACs, may not be predictable, even though administration of these drugs is reliable and easy. Clinicians should remember that, among the many interactions with other drugs, that can cause even extensive bleeding, NOACs also interact with some common antibiotics and antifungal medications and so a careful evaluation when choosing antibiotics is strongly suggested. Moreover, it is recommended to refer to the 2015 European Guidelines of the European Heart Rhythm Association before performing any surgical procedures.

**Introduction**
When “novel/new” oral anticoagulants entered the market, including Italy, a few years ago, their aim was replace the “old” Vitamin K antagonists. Oral anticoagulants have a number of clinical applications, and a very promising one of these is atrial fibrillation prophylaxis (AF). For a better understanding of what it means to have, as a pharmacological target, a system such as coagulation, it is necessary to start by pointing out how essential it is in a body with circulation. It is to be remembered that the main function of the coagulation system is hemorheological, consisting of ensuring blood circulation. This all happens due to the integrity of the vascular endothelium and the “natural” anticoagulant function of the heparin-like membrane molecules that interact with Antithrombin III, Factor Xa and other factors.

To maintain the circulation of blood physiologically, a not less important property is hemostasis, i.e. in the possibility of promptly blocking a hemorrhage caused by injury by forming a platelet plug. The damaged endothelial cells secrete the von Willebrand factor that helps the adhesion of the platelets; thereafter, the fibrinogen which cannot aggregate under normal conditions, in the case of injury is polymerized in fibrin to form a sort of mesh over the injury. This process can occur by two means which are defined intrinsic and extrinsic: the extrinsic pathway is faster because it requires a lower number of factors than the intrinsic pathway, which additionally requires some plasmatic factors, including FXII (Hageman factor). Later on, if the damage was only limited, it is repaired by the clot being reabsorbed and new endothelium being affixed. Coagulation proves to be a complex enzymatic system, activated in a cascade manner, and which presents many redundant aspects hard to control, to the extent that its pathological activation – resulting in thrombosis and embolism – has led to the development of molecules to control its function: the anticoagulant drugs (Figure 1). The novel oral anticoagulants (NOACs), or direct thrombin inhibitors, are, therefore, a new class of anticoagulants designed to prevent stroke and systemic embolism in non-valvular AF, a condition where there is significant prothrombotic stimulation. Given the high prevalence of AF (there are 33.5 million cases in the world) (1) and the general ageing of the population, it is quite likely that patients requiring dental treatment will simultaneously be undergoing anticoagulant treatment. So what should be done in the case of ongoing anticoagulant treatment?

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based on surgical needs, with particular reference to dental procedures.

The family of novel oral anticoaguants

There is now a family of novel oral anticoaguants – no longer new or novel apart from in the name retained in the acronym – which should more properly be referred to as Non-vitamin K Antagonist Oral Anticoaguants (NOACs). There are four pharmaceuticals currently on the market in Italy: dabigatran, apixaban, edoxaban and rivaroxaban (Figure 2). Dabigatran is a direct thrombin inhibitor which is reversible; apixaban, edoxaban and rivaroxaban, on the other hand, reversibly inhibit Factor Xa. Factor Xa is the key to convergence of the extrinsic and intrinsic pathways of coagulation (2). Selectively blocking the cascade factors of coagulation, these drugs impede the conversion of fibrinogen into fibrin strands, with an effective anticoagulant action. The pharmacokinetics of NOACs is referred to in Table 1. From the pharmacokinetics it emerges that NOACs are a valid alternative to treatment with warfarin or acenocumarol for preventing a thromboembolic event in patients affected by non-valvular AF and in the treatment/prevention of venous thromboembolism (3), owing to their non-interference with food and the lower interactions with other drugs. For all pharmaceuticals on the market, it is the major clinical trials that permit their approval and, to some extent, determine their success. The history of NOACs is no exception: their approval and marketing, which took place in 2013 (Official Gazette, general series 202, of 29 August 2013), are the result of the demonstrations of efficacy and safety resulting from comparative clinical studies with the old anticoaguants.

The first of the NOAC trials, the RE-LY (Dabigatran versus Warfarin in Patients with Atrial Fibrillation) showed that dabigatran, compared to warfarin, is able to reduce the rates of stroke and systemic embolism, with a similar or lower rate, depending on dosage, for major hemorrhage (4).

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) revealed a substantial parity of rivaroxaban and warfarin in stroke and embolism prevention and also for major hemorrhage in the two treatment groups (5).

The trial conducted for apixaban, ARISTOTLE (6) (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), showed that, compared to warfarin, it significantly reduces the risk of stroke, systemic embolism and major hemorrhage.
Lastly, the ENGAGE AF-TIMI 48 trial (7) (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction) demonstrated that edoxaban resulted in a significant reduction in major hemorrhaging compared to warfarin.

After the publication of the studies, the European Society of Cardiology published the first “Practical Guidelines” in 2013 as a supplement to the Atrial Fibrillation Guidelines for the safe and effective use of NOACs, with a later update in 2015. It should be noted that these first clinical trials excluded patients with prosthetic valves or with severe valvular stenosis, and that therefore, at the moment, NOACs are not indicated for this type of patient owing to the scarcity of data. Other patients for whom the use of NOACs is not yet consolidated are those with AF with biological heart valves or who have undergone valvuloplasty surgery. In this case, in clinical practice, the use of NOACs is often forced on the basis of general experience that, while waiting for the numerically significant data that can only come from large trials, has a positive response. No data are currently available on patients undergoing percutaneous valve repair/replacement (8). Lastly, another important area for the use of NOACs is in the treatment of deep vein thrombosis and pulmonary embolism, and preventing it from recurring in adults. All NOACs can be administered for treating acute pulmonary embolism and subsequently in the prevention of relapse (9).

Dental management of patients using NOACs

The dental management of patients undergoing anticoagulant treatment is now well established as regards warfarin or dicoumarol (10-11), but may not be so predictable as regards those patients taking NOACs. Although NOACs are drugs with an efficacy and safety profile that makes their use frequent, reliable and easy, it is to be remembered that, among the many interactions with other drugs, they also interact with some common antibiotics and antifungal medications (12). Recent clinical studies have shown that clarithromycin and rifampicin significantly impair the bioavailability of dabigatran, while clarithromycin, ...

Table 1 Main pharmacokinetic and pharmacodynamics data of oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>FXa</td>
<td>FXa</td>
<td>FXa</td>
<td>FXa</td>
<td>FII</td>
</tr>
<tr>
<td>Prodrug</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt;50%</td>
<td>66-100%</td>
<td>50%</td>
<td>6.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Dosage</td>
<td>OD</td>
<td>OD</td>
<td>BID</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>Time to max. eff</td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>1-2 hours</td>
<td>1-3 hours</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Half-life</td>
<td>10-14 hours</td>
<td>7-12 hours</td>
<td>12 hours</td>
<td>11 hours</td>
<td>40 hours</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>50%</td>
<td>33%</td>
<td>25%</td>
<td>80%</td>
<td>0%</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Anti Fxa</td>
<td>Anti Fxa</td>
<td>Anti Fxa</td>
<td>ECT, dTT, (aPTT)</td>
<td>INR</td>
</tr>
<tr>
<td>Interactions</td>
<td>P-gp</td>
<td>P-gp, BCRP, CYP3A4</td>
<td>P-gp, BCRP, CYP3A4</td>
<td>P-gp</td>
<td>Pharmaceuticals and food</td>
</tr>
<tr>
<td>Hepato-biliary metabolism</td>
<td>50% (3A4&lt;5%)</td>
<td>69% (3A4, 2J2)</td>
<td>75% (3A4)</td>
<td>20% (no 3A4)</td>
<td>&gt;90% (2C9)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>50%</td>
<td>90%</td>
<td>90%</td>
<td>35%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

OD = single daily administration
BID = twice daily administration
ECT= ecarin clotting time
plasma-diluted thrombin time (dTT)  aPTT = activated partial thromboplastin time
ml of 5% Tranexamic acid four times a day for up to 5 days to reduce any minor oral bleeding.

The discontinuation of NOAC therapy and its temporary substitution with low molecular weight heparin has no benefit as regards thromboembolism; on the contrary, it increases the risk of even greater bleeding. Data from the adverse event log have shown that the switch to heparin is still improperly used on patients undergoing NOAC therapy, and this leads to a significantly higher rate of periprocedural bleeding.

Dabigatran (13) and rivaroxaban (14) should be discontinued at least 24 hours before performing more complex oral surgery, such as extracting more than three teeth and/or in the case of maxillofacial surgery on patients at risk of excessive bleeding or altered hemostasis. Patients with severe renal impairment may, on the other hand, require a longer period of discontinuation than 24 hours since they have a significant increase in the maximum plasma concentration and a longer half-life (Table 2). Once interrupted, the treatment with rivaroxaban should not be resumed immediately after surgery, but usually 24-48 hours later. Regarding dabigatran, the decision to suspend the drug must be carefully discussed with the attending physician to avoid possible thromboembolic complications, and the same applies to apixaban and edoxaban about which there is less data in the literature.

In October 2015, approval was given to idarucizumab, a monoclonal antibody developed as an antidote to dabigatran, which can be used when it is necessary to reverse the anticoagulant therapy in an emergency or urgent situation (13). Lastly, it is worth remembering that the antagonist of the old oral anticoagulants is vitamin K.

<table>
<thead>
<tr>
<th>Types of operations</th>
<th>Low risk of bleeding</th>
<th>High risk of bleeding</th>
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<tr>
<td>Extraction of one to three teeth; periodontal surgery; incision of abscess; implantology</td>
<td>Perform the procedure 12-24 hours after the last dose. Resume the therapy once haemostasis is obtained or after 6 hours (skipping 1 of the BID administrations)</td>
<td>Suspend dabigatran 24 hours before surgery or for a longer period depending on the patient’s renal function and the risk of bleeding. Resume the medication 24 hours after surgery. Suspend rivaroxaban 24 hours before surgery or for a longer period depending on the patient’s renal function and the risk of bleeding. Resume the medication 24 hours after surgery. Suspend apixaban 24 hours before surgery. Resume the medication 24 hours after surgery. There are fewer indications regarding edoxaban.</td>
</tr>
</tbody>
</table>

Table 2 Therapeutic adaptation of NOACs for the main dental procedures (8;16)
Conclusion
Though the administration of NOACs is reliable and easy, in the dental management of patients taking these drugs, interactions, which could cause even extensive bleeding, are not an uncommon event. Therefore, a careful evaluation when choosing antibiotics is recommended and the appropriate should be referred to whenever performing any surgical procedures.

References