DEBATE Open Access

Managing patients taking novel oral anticoagulants (NOAs) in dentistry: a discussion paper on clinical implications

Fulvia Costantinides[1*], Roberto Rizzo[1], Lorenzo Pascazio[2] and Michele Maglione[1]

Abstract

Background: The aim of this paper is to contribute to the discussion on how to approach patients taking new orally administered anticoagulants (NOAs) dabigatran etexilate (a direct thrombin inhibitor), rivaroxaban and apixaban (factor Xa inhibitors), before, during and after dental treatment in light of the more recent knowledges.

Discussion: In dentistry and oral surgery, the major concerns in treatment of patients taking direct thrombin inhibitors and factor Xa inhibitors is the risk of haemorrhage and the absence of a specific reversal agent. The degree of renal function, the complexity of the surgical procedure and the patient's risk of bleeding due to other concomitant causes, are the most important factors to consider during surgical dental treatment of patients taking NOAs. For patients requiring simple dental extraction or minor oral surgery procedures, interruption of NOA is not generally necessary, while an higher control of bleeding and discontinuation of the drug (at least 24 h) should be requested before invasive surgical procedures, depending on renal functionality.

Summary: The clinician has to consider that the number of patients taking NOAs is rapidly increasing. Since available data are not sufficient to establish an evidence-based dental management, the dentist must use caution and attention when treating patients taking dabigatran, rivaroxaban and apixaban.

Keywords: Novel oral anticoagulants, Dabigatran, Rivaroxaban, Apixaban, Dental treatment

Background

In the last few years, new orally administered anticoagulants drugs (NOA) have been introduced in clinical practice for patients affected by various diseases and medical conditions that require use of extended-duration anticoagulant therapy (prophylaxis and treatment of pulmonary embolism and venous thrombosis, including prophylaxis after orthopaedic surgery; prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or prosthetic valves replacement; reduction of the risk of death, reinfarction and thromboembolic events after myocardial infarction) [1]. Similarly to subcutaneous or intravenously administered low-molecular-weight heparin (LMWH) and in contrast to coumarin derivatives (warfarin and acenocoumarol), these new medications interfere with very specific steps of the coagulation cascade. Three types of NOAs have recently been approved for use in the USA and in several European countries, including Italy. These are dabigatran etexilate, which acts as a direct thrombin inhibitor (DTI), rivaroxaban and apixaban that work as factor Xa inhibitors (FXaI). A fourth one FXaI, edoxaban, obtained the recent approval of the European Medicines Agency in Europe (April 2015, 23th) [2].

Advantages of dabigatran, rivaroxaban, apixaban and edoxaban have to be researched in their capacity to provide a stable anticoagulation at a fixed dose without the necessity to monitor the coagulation with routine laboratory exams (INR). They have a relatively rapid onset and reach peak concentration in few hours [3]. Furthermore, unlike vitamin K antagonists, they show a wide therapeutic margin, low drug- to- drug interactions and no significant food interactions [1, 4].

The progressive diffusion of NOAs has a direct repercussion on different dentistry specialties particularly in a surgical context. Because of their relatively recent

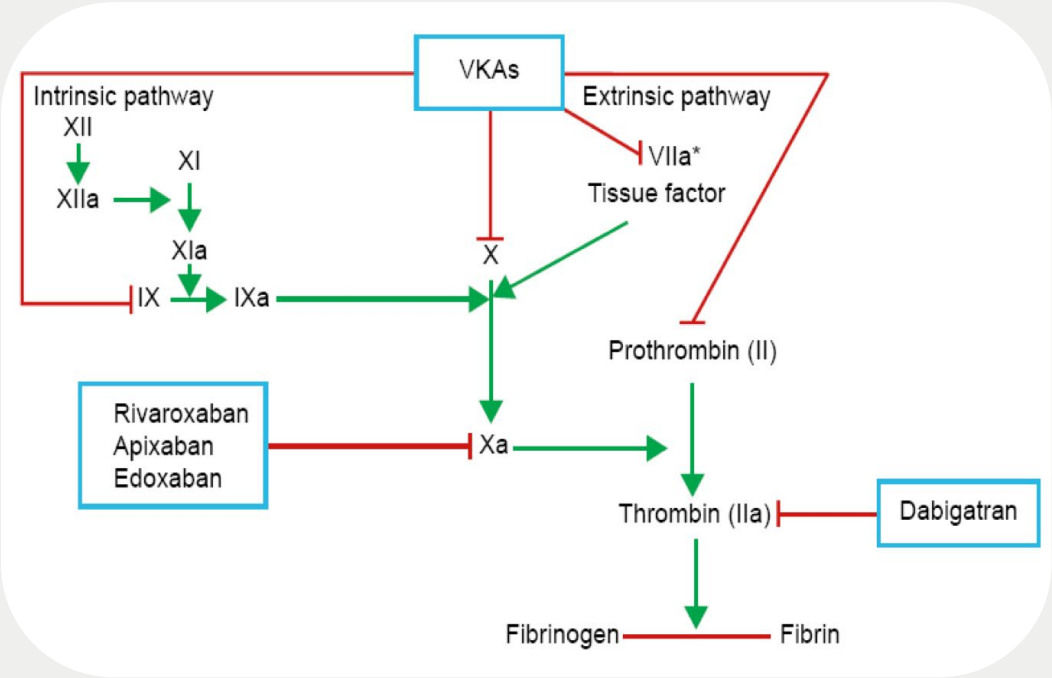
* Correspondence: f.costantinides@fmc.units.it
[1]School of Specialization in Oral Surgery, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
Full list of author information is available at the end of the article

Managing patients taking novel oral anticoagulant (NOAs) in dentistry : a discussion paper on clinical implication

SCAN ME

วิทยากร : ทพญ. เจนจิรา สงประเสริฐ

Non-Vitamin K antagonist oral anticoagulant drug (NOAs)



- **Dabigatran** : Direct thrombin inhibitor
- **Rivaroxaban**
- **Apixaban**
- **Edoxaban**

Direct factor Xa inhibitor

Non-Vitamin K antagonist oral anticoagulant drug (NOAs)

Advantage

- Provide a stable anticoagulation at fixed dose w/o INR monitor
- Rapid onset and peak concentration in few hours
- Wide therapeutic margin
- Low drug to drug interactions
- No significant food interactions

Dabigatran (Direct thrombin inhibitor)

- Rapid onset
- Peak plasma concentration at 0.5- 4 hours
- Excretion : Renal
- Half life
  - Healthy patients : 12-14 hours
  - Elderly patients : 14-17 hours
  - Severe renal dysfunction (Creatinine clearance < 15-30 ml/min) : 27 hours
- Dabigatran should be discontinued at least 24 hours before OMFS in severe bleeding risk patient

Minor bleeding

- Delay the next dose or discontinuation

Moderate - severe bleeding

- Mechanical compression
- Surgical intervention
- Fluid replacement
- Hemodynamic support
- Oral charcoal application
- Haemodialysis

Life-threatening bleeding

- Administration prothrombin complex concentration
- Charcoal
- Antidote : Idarucizumab (reverse in minute)

Dabigatran (Direct thrombin inhibitor)

Factors assessment of bleeding risk

- Patient-dependent factor e.g
  - Renal function
  - Congenital coagulation
  - Age
  - Antiplatelet drug
  - Anticoagulant drug

- Surgery dependent factor e.g
  - Invasiveness and difficulty of surgery

Patient dependent factor and surgery dependent factor must be considered together

Table 1 Guide to discontinuation of dabigatran before elective surgery; indications are matched for renal function and risk of bleeding (van Ryn et al. 2010) [9]

Cretinine clearance (ml/min)	Time of discontinuation before surgery for standard risk of bleeding	Time of discontinuation before surgery for high risk of bleeding[a]
>80	24 h	2–4 days
>50 to ≤ 80	24 h	2–4 days
>30 to ≤ 50	≥48 h	4 days
≤30[b]	2–5 days	5 days

[a]Determinants of bleeding risk are: type of surgery (cardiac, neural, abdominal, surgery involving major organs or requiring complete haemostasis), advanced age, comorbidities (i.e. major cardiac, respiratory, liver diseases) and concomitant use of antiplatelet therapy

[b]Dabigatran controindicated

Dabigatran (Direct thrombin inhibitor)

RE-LY trial .

Randromized group	Dose adjusted wafarin compare Dabigatran 150 mg and Dabigaran 110 mg	
	Dabigatran 150 mg	Dabigatran 110 mg
Stroke/ Systemic embolism	↓	no difference
Ischemc stroke	↓	no difference
Hemorrhagic stroke	↓	↓
Major bleeding	no difference	↓

Dabigatran (Direct thrombin inhibitor)

Drug interaction

- NSAID : increase risk of bleeding (Paracetamol or opioid are safer)

- P-glycoprotein 1 (P-gp 1) : inducer decrease plasma concentration of dabigatran e.g
  - Rifampicin
  - Dexamethasone
  - Carbamazepine

- P-glycoprotein 1 inhibitor (P-gp 1 inhibitor) : increase plasma concentration of dabigatran e.g
  - Ketoconazole single dose 400 mg : increase 135%
  - Clarithromycin (Moderate P-gp 1 inhibitor) : no effect on dabigatran concentration

Rivaroxaban (Direct factor Xa inhibitor)

- Rapid onset
- Peak plasma concentration at 2.5- 4 hours
- Oral administration once daily
- Half life
    - Healthy patients : 5.7- 9.2 hours
    - Elderly patients (older than 75 yr): 12- 13 hours

- No antidote
    - Some study suggest the use of **recombinant factor VIIa** or **active concentrate prothrombin complex** to antagonizing the anti coagulation effect

- Rivaroxaban should be discontinued at least 24 hours before OMFS in severe bleeding risk patient

- Severe renal impairment may necessitate discontinuation period > 24 hours

Rivaroxaban (Direct factor Xa inhibitor)

The Rocket AF trial.

Randromized group	Dose adjused warfarin compare Rivaroxaban
	Rivaroxaban
Stroke/ Systemic embolism	↓
Ischemc stroke	↓
Hemorrhagic stroke	↓
Intracranial Hemorrhage	↓

Rivaroxaban (Direct factor Xa inhibitor)

Drug interaction

- Strong CYP3A4 and P-gp inhibitor
  - Ketoconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
  - Clarithromycin

Increase serum concentration of rivaroxaban (should be avoid)

- CYP3A4 and P-gp inducer
  - Rifampicin
  - Erythromycin

Decrease serum concentration of rivaroxaban

- No report of interaction between rivaroxaban and amoxicillin, cephalexin cefazolin, clindamycin
- Antibiotic can be use safely
- No interaction between rivaroxaban and NSAIDs

Apixaban (Direct factor Xa inhibitor)

- Rapid onset
- Peak plasma concentration about 1-3 hours
- Excretion : bile
- Half life : 12 hours
- No antidote
    - Emergency situation ; some study suggest the use of **recombinant factor VIIa** or **active concentrate prothrombin complex** to antagonizing the coagulation
      (same rivaroxaban)

- **ARISTOTLE trial** : Apixaban Vs Warfarin
    - Decease major bleeding compare Warfarin
    - Decrease thromboembolic risk compare Warfarin

- **Drug interaction**
    - CYP3A4 and P-gp inhibitor are contraindication

Table 2 Principal characteristics of new oral anticoagulants (NOAs)

NOAs	Class	Indications	Dosage	Time to peak plasma concentration	Half life	Routes of elimination	Monitoring of coagulation
Dabigatran etexilate	Direct thrombin inhibitor	Prevention of cerebrovascular complications in non-valvular atrial fibrillation; hip and knee replacement surgery; venous thromboembolism prophylaxis and management	110 mg-150 mg twice daily	2–4 h	12–14 h; 14–17 h in elderly; 15–18 h in moderate renal impairment; up to 28 h in advanced renal impairment	80 % renal, 20 % hepatic	Not needed
Rivaroxaban	Direct inhibitor of factor Xa	Prevention of cerebrovascular complications in non-valvular atrial fibrillation; venous thromboembolism prophylaxis and management	20 mg daily	2.5–4 h	5–10 h; 12–13 h in patients > 75 years	66 % renal, 28 % in feces	Not needed
Apixaban	Direct inhibitor of factor Xa	Prevention of cerebrovascular complications in non-valvular atrial fibrillation; venous thromboembolism prophylaxis and management	5 mg twice daily	1–3 h	10–14 h	25 % renal, 55 % intestinal, remnant hepatic	Not needed

Thank you

Do you have any questions?