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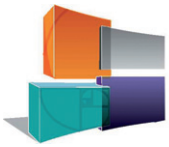

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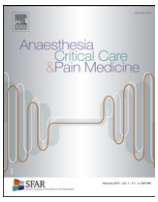

Recommendations

Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: Updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP) – September 2015

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ABSTRACT

Since 2011, data on patients exposed to direct oral anticoagulants (DOAs) while undergoing invasive procedures have accumulated. At the same time, an increased hemorrhagic risk during perioperative bridging anticoagulation without thrombotic risk reduction has been demonstrated. This has led the GIHP to update their guidelines published in 2011. For scheduled procedures at low bleeding risk, it is suggested that patients interrupt DOAs the night before irrespective of type of drug and to resume therapy six hours or more after the end of the invasive procedure. For invasive procedures at high bleeding risk, it is suggested to interrupt rivaroxaban, apixaban and edoxaban three days before. Dabigatran should be interrupted according to the renal function, four days and five days if creatinine clearance is higher than 50 mL/min and between 30 and 50 mL/min, respectively. For invasive procedures at very high bleeding risk such as intracranial neurosurgery or neuraxial anesthesia, longer interruption times are suggested. Finally, bridging with parenteral anticoagulation and measurement of DOA concentrations can no longer routinely be used.

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1. Introduction

In 2011, the GIHP published guidance for the perioperative management of direct oral anticoagulants (DOAs) [1,2], using a pragmatic approach. The proposals were conservative and cautious given the lack of experience on how to handle these molecules at that time.

Since 2011, experiences in the use of DOAs have accumulated and more patients have benefit of these drugs once they became available following approval [3]. Moreover, 10%–15% of these patients on anticoagulants require surgery or an invasive procedure every year.

Sub-analyses of large randomized trials [4–7] as well as large prospective registries have been published [8–10] together with biological follow-up and the add-on benefit of biological specific tests for clinical decision [11].

In addition to rivaroxaban (Xarelto®) and dabigatran (Pradaxa®), apixaban (Eliquis®) and edoxaban (Lixiana®) have been approved and an increased risk of bleeding have been reported in atrial fibrillation patients on vitamin K antagonists (VKA) or DOAs bridged to heparins (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) during invasive procedures with no benefit regarding thromboembolic risk [7,8,12,13].

The present update of the guidelines for the management of DOAs during the perioperative period of planned invasive procedures responds to the following objectives:

- to restrict preoperative bridging for rare situations to avoid perioperative bleeding;
- to reduce the time delay of DOAs interruption preoperatively to avoid thromboembolic events without increasing perioperative bleeding risk;
- to take into account the pharmacokinetic differences between DOAs (-xabans and dabigatran);
- to clarify the role of biological measurements in these specific situations.

Table 1 summarizes the perioperative management of DOAs. The following section provides a precise description of the different stages.

2. Low-risk hemorrhagic procedures

2.1. Low hemorrhagic risk

Low-risk hemorrhagic invasive procedures are defined according to the 2008 French National Authority for Health (Haute Autorité de santé) guidelines for the perioperative management of VKA [14] They correspond to invasive procedures associated with infrequent bleedings, of low intensity and easily managed, usually performed in patients treated with therapeutic doses of anticoagulants. They are as follows: cutaneous surgery, cataract surgery, low-risk hemorrhagic rheumatologic procedures, certain dental surgery and certain GI endoscopy procedures (non-exhaustive list). These procedures are performed without VKA interruption and can be performed on DOAs. Various societies have published guidelines for the management of invasive procedures in patients on DOAs: the French Society of Digestive Endoscopy, the French Society of Ophthalmology and the French Society of Oral Surgery.

2.2. Preoperatively management of DOAs

This is summarizes on Fig. 1 and applies irrespective of the dose regimen of DOA (Fig. 1).

If it is a twice daily regimen, the last intake of the DAO should be on the morning of the day before the planned invasive procedure. If it is a once daily regimen with an every morning intake, the last dose should be on the morning of the day before the planned invasive procedure. If it is a once daily regimen with an every evening intake, the last dose should be two days before the planned invasive procedure.

2.3. Bridging strategy and biological monitoring

In this case, preoperative bridging by UFH or LMWH is not recommended. There is no reason to measure the concentration of DOA before the procedure. The objective is to avoid high plasma concentrations of DOA during the procedure (but not to obtain negligible concentrations).

2.4. Resumption of DOAs

In the absence of ongoing bleeding and/or a surgical contraindication, DOA treatment can resume at least six hours after the end of the invasive procedure as follows (Fig. 1):

- the evening if once daily regimen with an evening intake;
- the next morning if once daily regimen with a morning intake;
- the evening of the same day if twice daily regimen.

If there is an ongoing bleeding or any surgical contraindication, the protocol of high-risk bleeding procedures applies and the resumption must be delayed and venous thromboprophylaxis

Table 1
Perioperative management of direct oral anticoagulants (DOAs) according to hemorrhagic risk.

GIHP Groupe d'intérêt en hémostase péri-opératoire	Low hemorrhagic risk	High hemorrhagic risk		
Before the procedure	No DOA the evening before and the morning of the procedure	Rivaroxaban Apixaban Edoxaban	Cockcroft ≥ 30 mL/min	Last DOA on D-3
		Dabigatran	Cockcroft ≥ 50 mL/min	Last DOA on D-4
			Cockcroft 30–49 mL/min	Last DOA on D-5
	No bridging No dosage			
After the procedure	Resumption at the usual time but at least 6 h after the procedure	"Prophylactic" dose of anticoagulant At least 6 hours after the procedure if venous thromboprophylaxis is indicated "Therapeutic" dose of anticoagulant as soon as the hemostasis allows it (between 24 and 72 hours)		

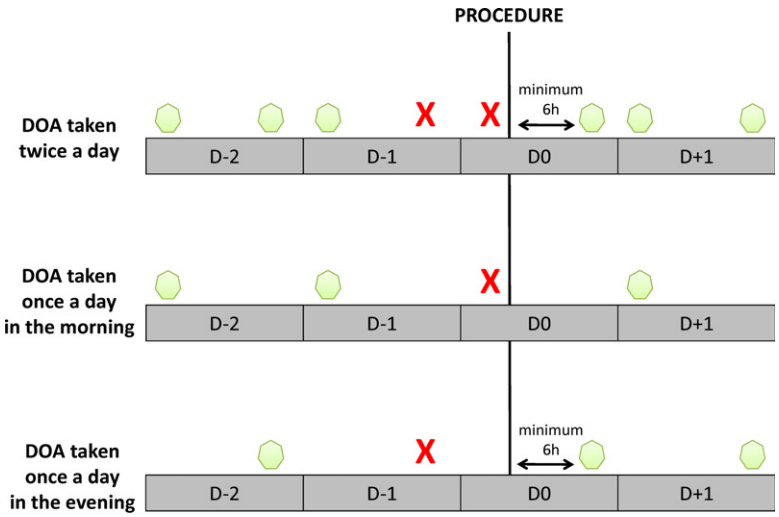

Fig. 1. Invasive procedures with low hemorrhagic risk.

(mechanical or pharmacologic) should be started according to the risk of venous thromboembolic event.

3. High hemorrhagic risk procedures

3.1. High hemorrhagic risk procedures

These procedures cannot be reasonably performed on anticoagulant [15] as surgical haemostasis cannot be performed safely and there is a need for a window without anticoagulant. These procedures are sometimes artificially separated as "procedures at moderate hemorrhagic risk" and "procedures at major hemorrhagic risk" [16].

3.2. Preoperative management

It is summarizes in Table 1. Timing of interruption is according to creatinine clearance (CrCl Cockcroft and Gault formula), age and concomitant drugs that may increase DOA plasma concentrations (P-glycoprotein inhibitors for all DOAs, cytochrome CYP3A4 inhibitors for xabans) (Table 2).

The proposed protocol applies irrespective of the type of xaban drugs owing to the major pharmacokinetic similarities of these drugs. The last intake should be three days before the procedure (day 0 being the day of the procedure) when creatinine clearances is higher than 30 mL/min. Due to the predominant renal elimination of dabigatran, this time window should be increased up to 5 days if CrCl is between 30 and 50 mL/min and to four days if Cr CL is above 50 mL/min. This assumes that a recent creatinine level is available [17].

3.2.1. Very high hemorrhagic risk procedures

Very high hemorrhagic risk such as intracranial neurosurgery or neuraxial anesthesia/puncture needs a longer interruption time of DOAs prior to the planned procedure up to five days for xabans and dabigatran in the absence of renal failure. If needed, biological monitoring of DOA may be considered.

The entire group strongly recommends not performing spinal or epidural anesthesia or deep-block techniques in patients with a possible DOA concentration (insufficient discontinuation time), in particular in patients on dabigatran over 80 years of age or in renal failure.

Table 2
Indications and usual DOA posologies.

	Dabigatran Pradaxa®	Rivaroxaban Xarelto®	Apixaban Eliquis®	Edoxaban Lixiana®
VTE prophylaxis after major orthopedic surgery	220 mg OD or 150 mg OD if: CrCl 30–50 mL/min, P-gp inhibitors, age ≥ 75 years	10 mg OD	2.5 mg BID	Not indicated in Europe
	THR: 28–35 days TKR: 10 days	THR: 5 weeks TKR: 2 weeks	THR: 32–38 days TKR: 10–14 days	
Treatment of VTE Long-term prevention of VTE	150 mg BID 110 mg BID if: age ≥ 80 years or verapamil	15 mg BID (3 weeks) then 20 mg OD	10 mg BID (7 days) then 5 mg BID (then 2.5 mg BID to prevent recurrence after 6 months of treatment for DVT or PE)	60 mg OD or 30 mg OD if: CrCl 15–50 mL/min, wt. ≤ 60 kg, P-gp inhibitors
Stroke prevention in non-valvular AF	150 mg BID or 110 mg BID if: age ≥ 80 years or verapamil	20 mg OD or 15 mg OD if: CrCl 30–49 mL/min	5 mg BID or 2.5 mg BID if: 2 criteria: age ≥ 80 years, wt. ≤ 60 kg, creatinine ≥ 133 μmol/L	60 mg OD or 30 mg OD if: CrCl 15–50 mL/min, wt. ≤ 60 kg, P-gp inhibitors

DOA: direct oral anticoagulant; VTE: venous thromboembolism; OD: once a day; BID: twice a day; THR: total hip replacement; TKR: total knee replacement; DVT: deep venous thrombosis; PE: pulmonary embolism; CrCl: creatinine clearance according to the Cockcroft and Gault formula; AF: atrial fibrillation; P-gp: P-glycoprotein.

3.2.2. Early phase of a venous thromboembolic event

If planned procedure should take place during the early phase of deep venous thrombosis or pulmonary embolism when high dose of rivaroxaban or apixaban are recommended, a personalized approach should be discussed by a multidisciplinary team and the proposed protocol cannot apply.

3.3. Bridging and biological monitoring

There is no need for preoperative heparin bridging (UFH or LMWH) except for very thrombotic high-risk. Similarly, there is no need for biological monitoring when the recommended interruption periods are applied and there is no additional risk of drug accumulation.

3.4. Resumption of anticoagulation and preventive measure for venous thromboembolic risk

If venous thromboprophylaxis is indicated (risk related to surgery, individual risk factors), heparin (UFH or LMWH) or fondaparinux is administered at least six hours after the end of the invasive procedure.

DOAs at a prophylactic dose can be prescribed within the approved indications (total hip or knee arthroplasties) with care to avoid overlapping the change in molecules.

When surgical hemostasis is obtained and in the absence of an epidural catheter, the initially prescribed DOA can be resumed. A "therapeutic" dose of anticoagulant can usually be foreseen between 24 and 72 hours postoperatively. This first "therapeutic" dose is administered 12 hours after the last "prophylactic" LMWH administration.

In the presence of an epidural catheter, therapeutic anticoagulation must be administered with heparin in order to safely withdraw the catheter (there are specific guidelines for the management of epidural catheters in case of prophylactic anticoagulation doses that do not apply to higher doses of DOAs [18]).

Creatinine clearance should be monitored postoperatively if the invasive procedure and/or medical condition of the patient could affect renal function and the dose regimen of DOA should be titrated accordingly.

4. Conclusion

This update suggests shortening the preoperative periods for interruption of DOAs to ensure a DOA concentration compatible with a safe haemostasis during and immediately after an invasive procedure without the need for bridging with parenteral anticoagulation. The proposed postoperative resumption takes into account the risk of bleeding, the type of medication, and the venous and arterial thromboembolic risk.

Disclosure of interest

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