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Management of Direct Oral Anticoagulants in the Perioperative Setting

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AN INCREASING NUMBER of patients undergoing surgical procedures are treated chronically by oral anticoagulants (OAC). Vitamin K antagonists (VKAs) have been standard practice in chronic anticoagulant therapy for decades. Despite a proved efficacy, they have several disadvantages. Over the past 5 years, direct oral anticoagulants (DOAs) such as dabigatran, rivaroxaban, apixaban, and edoxaban have been approved for several indications for long-term anticoagulation. Consequently, with the aging population and the extension of the indication of anticoagulation for stroke prevention in nonvalvular atrial fibrillation (AF), there are more cardiovascular risk patients who receive these new agents. In the medical setting, DOAs may be a suitable alternative to VKAs for stroke prevention in many patients because, among other advantages, there is no need for regular monitoring, their onset of action is faster, and there is less drug or food interaction. However, dose adjustments may be required for some patients with severe renal impairment and in some clinical settings. Even though DOAs have advantages over VKAs, perioperative management of patients treated with these agents remains challenging in several clinical situations, including elective or emergency surgical procedures, bleeding, overdose, and trauma. The present review will focus on the management of these patients during the perioperative period.

DIRECT ORAL ANTICOAGULANTS: APPROVED INDICATIONS

There are 3 main indications for DOAs: (1) Prophylaxis of venous thrombosis after orthopedic surgery (low dosage), (2) prevention of stroke in patients with nonvalvular AF, and (3) treatment of deep venous thrombosis and/or pulmonary embolism (these 2 last indications with higher dosage). Other indications are still under investigation. For example, low doses of DOAs have been investigated in combination with antiplatelet agents after acute coronary syndromes.[1] Consequently, a rapid increase in the number of patients treated by these new drugs is to be expected. Nevertheless, recent negative data[2] on anticoagulation of patients with mechanical valvular prosthesis reminds practitioners that only approved indications should be applied and that fixed doses of anticoagulant for everybody in all clinical settings cannot be as easy as they hoped.[3] Thus, in terms of number of patients, the principal indication of DOAs will remain essentially the prevention of stroke in AF.

COMPARISON WITH VKAS AND CLINICAL RELEVANCE FOR ANESTHESIOLOGISTS

Data from randomized, phase III trials of the DOAs indicate that these drugs are at least noninferior to warfarin for the prevention of stroke and systemic embolism in patients with AF.[4–7] Several meta-analyses have drawn the same conclusions: A favorable risk-benefit profile with significant reductions in stroke, intracranial hemorrhage, and mortality and with similar major bleeding as for warfarin but with increased gastrointestinal bleeding.[8–10]

Recent data have shown that around 15% to 25% of patients under DOAs for AF will have an invasive procedure within 2 years.[11] It is not surprising since AF prevalence increases with age (around 10% in octogenarians), and age increases the risk of undergoing surgery. A recent registry evaluating the perinterventional DOA management in unselected patients has reported interesting epidemiologic characteristics: Median age of 74 years, stroke prevention in AF as the main DOA indication (81%), and frequent impaired renal function (in 14.5%, defined as a glomerular filtration rate [GFR] of <50 mL/min).[12] Similar kinds of patient characteristics have been reported in other studies.[8–11] Even though the cost-effectiveness analysis is beyond the scope of this review, physicians must be aware of the increased risks in older patients.[13,14] Several risk-stratification scoring systems to assess risk of stroke ($CHADS_2$; CHA_2DS_2-VASc)[15,16] and bleeding (HAS-BLED; $HEMORR_2HAGES$)[17,18] have been developed; all of them included advanced age as a risk factor. Regardless of the medication chosen (VKAs or DOAs), old patients with AF must be treated cautiously, given the increased risk of stroke and bleeding and the potential challenges related to drug interactions and monitoring requirements.[13,14,19] The perioperative period is particularly critical for these patients.[20,21]

From a practical point of view, anesthesiologists must be aware of all developments about these new agents: Approved indications, pharmacologic properties (with proper advantages and limits), as well as current absence of antidotes and monitoring. Indeed, in the perioperative setting, major concerns

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for this class of drug are the risks of bleeding and the lack of an effective agent to rapidly reverse anticoagulation.[20–23]

MAJOR COMPLICATIONS AND PITFALLS EXPERIENCED IN THE LITERATURE

A few months after FDA approval of dabigatran for stroke prevention in nonvalvular AF (October 2010), a French team raised concerns on dabigatran administration in elderly patients in 2 cases, including 1 fatal.[24] These 2 cases highlighted the necessity of caution when treating "borderline" patients: Low body weight, very old age, and altered renal function. It is crucial when they are considered for invasive procedures.

Until the present time, 2 large registries have been published with perioperative data in patients treated with DOAs.[11,12] The first one is a post-hoc analysis of RE-LY study including 4,591 patients undergoing 7,637 procedures.[11] The last dose of dabigatran was given 49 (35-85) hours before the procedure, in comparison with 114 (87-144) hours for the last dose of warfarin. Heparin bridging was more frequent in the warfarin group than in the dabigatran one (28.5% *v* 15.3% and 17% in the 110-and 150-mg groups, respectively, $p < 0.001$). The main result was that dabigatran and warfarin were associated with similar rates of periprocedural bleeding, including patients having emergency surgery. These reassuring conclusions must be taken with caution because procedures were mainly at minimal or minor risk of bleeding and also because in the warfarin group, patients undergoing urgent surgery were not treated by prothrombin complex concentrates (PCC). The second registry evaluated the peri-interventional DOA management in unselected patients.[12] Out of 2,179 patients, 595 underwent 863 procedures (with a bleeding risk assessed as major in only 10.1% of the cases). Procedures were performed in patients receiving rivaroxaban (76%), dabigatran (23.5%), or apixaban (0.5%). DOA was continued, temporarily interrupted without heparin bridging, or interrupted with heparin bridging in 187, 419, and 257 cases, respectively. The use of heparin bridging significantly increased with the severity of the surgical procedure. In cases of DOA interruption, the median duration of DOA-free intervals was 2 days before (interquartile range [IQR]: 2) and 1 day (IQR: 3) after the procedure. Major cardiovascular events occurred in 1.0% and major bleeding complications in 1.2%. Major procedures were an independent risk factor for cardiovascular events and for major bleeding complications; when major procedures were assessed separately, heparin bridging was not an independent risk factor for major bleeding. These results suggest that peri-interventional DOA management mainly should be determined by the type of procedure. Continuation or short-term interruption of DOA may be a safe strategy for most minimal or some minor procedures. Nevertheless, patients at cardiovascular risk undergoing major procedures may benefit from heparin bridging, but bleeding risk needs to be considered.[20,22,25,26]

Another interesting recent post-hoc analysis from the ROCKET trial reported outcomes within 30 days after discontinuation of rivaroxaban or warfarin in patients with nonvalvular AF.[27] After temporary interruptions (median: 6 days), the rates of stroke and systemic embolism increased to 5 to 6 per 100 patient-years in both groups, suggesting that even with short temporary interruptions, the protection from anticoagulant therapy for AF is lost. Furthermore, patients transitioning to open-label VKA therapy at the end of the study had more strokes with rivaroxaban versus warfarin.[27] This result could be explained by the short half-life of rivaroxaban (as with the other DOAs) and that it took longer to reach a therapeutic international normalized ratio (INR) with rivaroxaban versus warfarin. Altogether, these data suggest that it seems wise to minimize the period of discontinuation.

PHARMACOKINETIC PROPERTIES OF THE DOAs

A complete review of pharmacokinetics of DOAs is beyond the scope of this article. Still, as all physicians, anesthesiologists must know of the main properties of these agents and their differences with VKAs in order to optimize the peri-procedural management of such patients.[20,22,23,28,29] The main features of pharmacokinetics of the DOAs are summarized in Table 1, and the main differences with VKAs are shown in Table 2. These differences have important clinical implications.

Even though drug-drug interactions are less important with the DOAs than with VKAs, significant variations in plasma levels have been described with drugs altering metabolism of DOAs, such as CYP3A4 inhibitors/inducers and P-gp inhibitors/inducers (Table 1).[28] CYP3A4 is partly involved in rivaroxaban and apixaban hepatic clearance. Another important interaction mechanism for DOAs (except for rivaroxaban) consists of significant resecretion over a P-glycoprotein

Table 1. Pharmacokinetics of the New Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Action	IIa inhibitor	Xa inhibitor	Xa inhibitor	Xa inhibitor
Administration	Twice daily	Once daily	Twice daily	Once daily
Bioavailibility	3%-7%	60% without food 100% with food	50%-60%	60%-65%
Plasma peak level after ingestion	2 h	2-4 h	1-4 h	1-2 h
Half-life	12-14 h	5-9 h (young) 11-13 h (elderly)	8-15 h	9-11 h
Renal excretion	80%	35%	25%	50%
Protein binding	35%	>90%	87%	
P-gp transporter interaction	++	+	+	?
Interaction CYP3A4	-	+	+	?