British Journal of Anaesthesia **111** (S1): i96–i113 (2013)
doi:10.1093/bja/aet401

BJA

REGIONAL ANAESTHESIA

New oral anticoagulants and regional anaesthesia

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Editor's key points

- Novel oral anticoagulants have been approved recently that impact the performance of regional anaesthesia.
- Recommendations differ in their guidance on timing for regional anaesthesia relative to anticoagulant discontinuation and resumption.
- Anaesthetists must balance the risks of bleeding with thrombotic complications based on drug pharmacokinetics and patient-dependent risk factors.

Summary. The new oral anticoagulants are approved for a variety of clinical syndromes, including the prevention of stroke in atrial fibrillation, acute coronary syndromes, treatment of venous thromboembolism (VTE), and prevention of venous thrombosis after total joint surgery or hip fracture. Published guidelines have differing recommendations on the safe interval between discontinuation of the anticoagulant and performance of neuraxial procedures and between the interventional procedure and redosing of the drug. While two to three half-life intervals might be acceptable in patients who are at high risk for VTE or stroke, an interval of four to six half-lives between discontinuation of the drug and neuraxial injections is probably safer in most patients at low risk of thrombosis. In those with renal disease, the interval should be based on creatinine clearance. After a neuraxial procedure or removal of an epidural catheter, anticoagulants can be resumed within 24–48 h in most patients, but they can be taken sooner in patients who are at higher risk for VTE or stroke, that is, 24 h minus the time to peak effect of the drug. The new antiplatelet drugs prasugrel and ticagrelor should be stopped 7 or 5 days, respectively, before a neuraxial injection and can be restarted 24 h later. In selected situations, laboratory monitoring of the anticoagulant effect is appropriate, and reversal agents are suggested when there is a need to rapidly restore haemostatic function.

Keywords: anaesthesia, regional; blood, anticoagulants; drug, safety

In 2010, the American Society of Regional Anesthesia (ASRA) and the European and Scandinavian Societies of Anaesthesiology published guidelines for regional anaesthesia in patients on anticoagulants.[1–3] However, several new oral anticoagulants have been approved by the US Food and Drug Administration (FDA) since these guidelines appeared: dabigatran in 2010; rivaroxaban and ticagrelor in 2011; and apixaban in 2012. Dabigatran is a direct thrombin inhibitor, rivaroxaban and apixaban are factor Xa inhibitors, while ticagrelor is a platelet adenosine diphosphate (ADP) P_2Y12 receptor inhibitor. Recent reviews of these anticoagulants discuss the development and risk of venous thromboembolism (VTE), options for thromboprophylaxis, and indications and pharmacokinetics of the drugs.[4–8] The European Society of Anaesthesiology discussed the new anticoagulants in their guidelines and their recent review of severe perioperative bleeding.[2 9] A Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis suggested adjustments to the interval between discontinuation of the drugs and performance of neuraxial procedures, based on the degree of risk of thrombosis.[10] Four reviews published this year focused on creatinine clearance (CrCl) in determining the interval between discontinuation of anticoagulant and subsequent neuraxial procedures.[11–14] Other recent reviews examined laboratory monitoring of anticoagulant activity of new anticoagulants and their reversal.[15–20]

In this review, we discuss topics related to the perioperative management of patients treated with the new anticoagulants. Our discussion will include efficacy of the drugs in specific clinical syndromes, the basis for the interval between discontinuation of anticoagulant and neuraxial procedures and between neuraxial injections and resumption of anticoagulant, laboratory monitoring of anticoagulant effect, and reversal of anticoagulant in the case of emergency interventions. Understanding clinical indications for the drugs will make the anaesthesiologist more aware of the risks of discontinuation. Knowledge of appropriate coagulation assays and agents available for drug reversal is required in cases of emergency surgery, haemorrhage, overdose, or planned neuraxial injections. We include the new antiplatelet drugs prasugrel and ticagrelor, since these were not discussed in recent reviews of new anticoagulants.

Approval for clinical use of new anticoagulants

The US FDA has approved new oral anticoagulants for prevention of VTE after total joint surgery and hip fracture, prevention of embolism in patients with atrial fibrillation, and treatment of active VTE (Table 1). Warfarin therapy has traditionally been used in these conditions but has the limitation that only 60% of patients have an international normalized ratio (INR) of 2.0–3.0, the recommended therapeutic range, at any given time during treatment.[21]

Reduction of bleeding and thrombotic complications when neuraxial procedures are planned

In all patients, evaluation for bleeding and thrombotic risk is essential. A bleeding tendency is suspected if there is a previous history of surgical or trauma-related haemorrhage, hepatic or renal disease, nutritional deficiency, or treatment with dual anticoagulant therapy (oral anticoagulant and antiplatelet agent). The use of a scoring system such as HAS-BLED[22] or HEMORR$_2$HAGES[23] might be helpful. Patients with a CHADS$_2$ score >2 are at increased risk of thrombosis.[24] Deciding when to discontinue an anticoagulant should take these risk factors into consideration.

To reduce the risk of bleeding or thrombotic complications in patients receiving new oral anticoagulants, it has been recommended that elective procedures requiring neuraxial anaesthesia should be delayed if[24]

(i) A thrombotic event [VTE, myocardial infarction, transient ischaemic attack (TIA), or stroke] has occurred within the previous 3 months;
(ii) A major haemorrhage, defined as a decrease in haemoglobin of 2 g dl^{-1}, transfusion of 2 units of packed red blood cells, or bleeding into an organ, has occurred within the previous 3 months; or
(iii) The patient is pregnant or <6 weeks post-partum.

Pharmacokinetics of drugs in relation to drug discontinuation and redosing

For older anticoagulants, the interval between discontinuation of anticoagulant and performance of a neuraxial injection was based on published studies. These include the time for synthesis of clotting factors after warfarin is discontinued,[25] risk factors for development of spinal haematoma after lumbar puncture and resumption of heparin,[26] and absence of spinal haematoma after neuraxial injection in patients treated with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs),[27–30] or subcutaneous heparin.[31]

For the new oral anticoagulants, the time between drug discontinuation and neuraxial injection is based on pharmacokinetic half-life. It has been recommended that two half-lives are an adequate compromise between safety, that is, avoidance of spinal haematoma and prevention of VTE.[32] The European and Scandinavian guidelines adopted two half-life intervals between discontinuation of the drug and neuraxial injection.[2 3] There are several reasons for this recommendation. The presence of residual anticoagulation facilitates transition to full anticoagulation after the procedure.[5] Because subclinical deep vein thrombosis occurs in ~15–20% of patients soon after surgery[33] and pulmonary embolism has been noted during the initial phase of warfarin therapy,[34] having residual anticoagulant might prevent perioperative VTE. It is, therefore, important to identify the earliest safe interval between discontinuation of drug and neuraxial injection or epidural catheter placement and between catheter removal and subsequent drug administration.[35]

Are two half-life intervals between discontinuation of anticoagulant and subsequent neuraxial injection adequate to provide protection against thrombosis, but not provoke bleeding? When a drug is discontinued, its disappearance from plasma depends on its half-life. After 1–6 half-lives, the following

Table 1 New anticoagulant drugs approved by the US FDA. AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis. *Approved indication, references: Garcia and colleagues,[16] Siegal and Cuker,[17] and Siegal and Crowther.[18] †Efficacy of dabigatran in studies not uniform (see text). ‡Efficacy when added to antiplatelet therapy. ¶Apixaban is non-inferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) in the treatment of acute VTE (from Agnelli and colleagues)[107]

Drug	Mechanism of action	Efficacy in clinical syndromes	Approved indications*
Dabigatran (Pradaxa®)	DTI	Prevention of postoperative VTE after total joint surgery† Prevention of stroke in AF Treatment of acute VTE	Prevention of stroke in patients with non-valvular AF (USA, Canada, and Europe) Prevention of VTE after knee or hip arthroplasty (Europe and Canada)
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE Acute coronary syndromes‡	VTE prophylaxis and stroke prevention in non-valvular AF (USA, Canada, and Europe) Treatment of VTE (USA, Europe, and Canada) Prevention of VTE after orthopaedic surgery (USA, Europe, and Canada)
Apixaban (Eliquis®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE¶	Stroke prevention in patients with non-valvular AF (USA, Europe, and Canada) VTE prophylaxis after hip and knee arthroplasty (Europe and Canada)