RECENT ADVANCES

Newer oral anticoagulants in perioperative settings

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ABSTRACT

Newer oral anticoagulant agents (NOACs) have several potential merits over previously used vitamin K antagonists (VKAs) during the perioperative period, including a wider therapeutic index, higher efficacy, quicker onset and offset of action, high oral bioavailability, less need for monitoring, reduced variability in dose response and drug/dietary interactions and less adverse effects. These oral anticoagulants have discrete targets within the coagulation pathway. The patients on these drugs often present to anesthesiologists for routine or emergency surgery, hence the awareness of the pharmacological profile of these newer drugs is imperative to attain its optimal response. This update describes some of the new generation oral anticoagulants and focuses on its merits and demerits in the existing perioperative settings.

Key words: Oral anticoagulant agents; Perioperative; Anticoagulants; Venous thromboembolic events; Atrial fibrillation

Citation: Kapoor D, Sandhu H, Singh M. Newer oral anticoagulants in perioperative settings. Anaesth Pain & Intensive Care 2014;18(1):116-118

INTRODUCTION

Oral anticoagulants have been used routinely for the prevention of deep vein thrombosis, pulmonary embolism, myocardial infarction and other thrombotic complications. Patients on anticoagulants may present for elective or emergency surgical procedures and require perioperative management of their coagulation status to prevent bleeding complications. Compounds targeting specific points in the coagulation pathways, e.g. low molecular weight heparins (antithrombin III), Fondaparinux (indirect Factor Xa inhibitor), Argatoban (direct thrombin inhibitor) have been developed for parenteral use as a bridging therapy. Oral agents with advantages of a wider therapeutic index, less need for monitoring, less variability in dose response as well as lower chances of drug/dietary interactions, may offer significant benefit over vitamin K antagonists (VKAs).

NEWER ORALLY ACTIVE ANTICOAGULANTS (NOACS)

Apixaban

Apixaban (Eliquis®, Pfizer Inc.) has been recently introduced in India for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Apixaban is a direct acting, reversible factor Xa inhibitor approved by United States Food and Drug Administration (FDA) for reducing the risk of stroke, systemic embolism in patients with non-valvular atrial fibrillation. This drug is available as oral formulations of 2.5 and 5 mg with elimination half-life of 12 hours with rapid oral absorption (66% bioavailability). No routine monitoring is required during administration. It has 25% renal and 55% fecal elimination.[1,2] No dose adjustment is required in mild or moderate renal impairment but should be used with caution in severe renal and hepatic impairment and/or associated coagulopathy. Anti-factor Xa assay, prothrombin time (PT) may be done when clinically indicated.[3] Several randomized control trials and a recent meta-analysis have displayed superiority of apixaban in preventing VTE in patients undergoing elective knee and hip replacement surgeries with similar bleeding rates.[4-7] Two large randomized controlled trials compared apixaban with aspirin and warfarin respectively, and established efficacy of apixaban in patients with atrial fibrillation (AF) requiring chronic anticoagulation.[8] Subsequently, a systematic review comprising six high quality clinical trials suggested its competence in patients

with AF.[9] Another trial evaluated apixaban against placebo in patients receiving aspirin and antiplatelet drugs after acute coronary syndrome but was terminated early due to 150% increased rate of major bleeding events without a significant reduction in recurrent ischemic events.[10]

Rivaroxaban

Rivaroxaban is another direct factor Xa inhibitor approved by FDA for prophylaxis and treatment of deep vein thrombosis(DVT) and pulmonary embolism in patients undergoing elective knee and hip replacement surgery and was approved for stroke prophylaxis in patients with non-valvular AF.[11] It is available as 10 mg tablets with once daily dosing and is recommended for 12 days following knee and 35 days following hip replacement respectively.[12-14] It's oral bioavailability is nearly 100% and elimination half life is 5-9 hours. Its use should be avoided in patients with moderate to severe hepatic impairment (Child Pugh B or C) and in patients with reduced creatinine clearance. Several randomized controlled trials support its use in the management of VTE and non-valvular AF.[15]

Dabigatran

Dabigatran is a direct thrombin inhibitor and is prescribed for managing the patients suffering from stroke, for prevention of systemic embolization in patients with AF and for treatment of VTE.[16,17] Its elimination half-life is 12-17 hours with 80% renal elimination. The major side effects are gastrointestinal (GI) bleeding, dyspepsia, nausea and diarrhea.[18]

NOACS IN PERIOPERATIVE SETTINGS

Preoperative

No published data exist on optimal perioperative management of newer oral anticoagulants. Nevertheless in a patient presenting for an emergency surgery, anesthesiologist must anticipate the risk of bleeding while administering neuraxial anesthesia. If the surgical procedure is deemed urgent, the surgery can be delayed 24-36 hours. In the setting of an elective surgery the management of NOACs is dependent on patient's renal function and procedure related risk of bleeding as described in Table 1.[19]

Post-procedure

In the setting of a low bleeding risk surgery NOACs can be resumed 24 hours postoperatively, while one must wait at least 48 -72 hours after a high risk surgery for resumption. In either case adequate hemostasis must be obtained before re-institution of therapy.[19]

Laboratory testing in perioperative settings

The routine perioperative monitoring of anticoagulation is not required during administration of NOACs due to rapid offset of action and a predictable pharmacokinetic profile. However, when laboratory confirmation is required, activated partial thromboplastin time (aPTT) and thrombin time (TT) can be used to rule out residual anticoagulation while using dabigatran. The routine laboratory tests like PT, aPTT are unreliable to predict anticoagulant effect of apixaban and rivarobaxan. Anti Factor-Xa assays can be done when clinically warranted.[3,19,20]

Perioperative bridging therapy for NOACs

The routine bridging of NOACs is not required due to rapid clearance and quick onset of effect upon re-institution of therapy. Nevertheless, bridging therapy is indicated with a low dose low molecular weight eparin e.g. Enoxaparin 40 mg OD, in the setting of bowel/gastric resection when oral intake is not possible.[19]

Table 1: Suggested management approach for interruption of NOACs[19]

Drug (dose) (CrCl= Creatinine clearance)	Half-life (hours)	Low bleeding risk surgeries (2 or 3 drug half-lives between last dose and surgery)	High bleeding risk surgeries* (4 or 5 drug half-lives between last dose and surgery)
Apixaban (5mg BD) CrCl>50ml/min	7-8	Last dose: 2 days before surgery (skip 2 doses)	Last dose: 3 days before surgery (skip 4 doses)
Apixaban (5mg BD) CrCl<50ml/min	17-18	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 4 days before surgery (skip 6 doses)
Rivaroxaban (20 mg OD) CrCl>50ml/min	8-9	Last dose: 2 days before surgery (skip 1 dose)	Last dose: 3 days before surgery (skip 2 doses)
Rivaroxaban (20 mg OD) CrCl=15-29.9 ml/min	9	Last dose: 2 days before surgery (skip 1 doses)	Last dose: 3 days before surgery (skip 2 doses)
Rivaroxaban (20 mg OD) CrCl= 30-0 ml/min	9-10	Last dose: 3 days before surgery (skip 2 doses)	Last dose: 4 days before surgery (skip 3 doses)
Dabigatran (150mg BD) CrCl>50ml/min	14-17	Last dose: 2 days before surgery (skip 2 doses)	Last dose: 3 days before surgery (skip 4 doses)
Dabigatran (150mg BD) CrCl=30-50ml/min	16-18	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 4-5 days before surgery (skip 6-8 doses)

**Examples of high bleeding risk surgeries: neurosurgery, cardiothoracic, major vascular, prostate/bladder surgery, renal biopsy, colonoscopy with polypectomy.*

DRUG INTERACTIONS & ONTRAINDICATIONS

All NOACs serve as a substrate for p-glycoprotein transport system, which prevents absorption and inhibits their secretion. Commonly used drugs like amiodarone, macrolides, verapamil and naproxen inhibit p-glycoprotein system and increase risk of bleeding. Thus concomitant administration of these agents must be avoided. Similarly the co-administration of rivaroxaban is contraindicated with protease inhibitors and azoles, both being strong CYP3A4 and p-glycoprotein inhibitors. All NOACs have significant renal excretion and are thus avoided in chronic kidney disease stage 4 and 5. They are also avoided in elderly patients >75 years of age, especially with compromised renal function. The food inter action of NOACs is clinically insignificant.[20]

CONCLUSION

The NOACs offer clear benefit over VKAs in terms of efficacy, quicker onset and offset of action, high oral bioavailability, less need for monitoring treatment and lesser adverse effects. The patients on these drugs might frequently present to anesthesiologists for routine or emergency surgery. Knowledge about their pharmacokinetics and drug interactions is thus essential for optimal perioperative management of therapy with NOACs. Although there is no study with direct comparison of NOACs, apixaban shows clear benefit in terms of adverse events. It also offers a considerable benefit in patients with renal insufficiency owing to its minimal renal excretion. However, further studies are warranted to establish their clinical benefits and formulate guidelines for their perioperative use.

Source(s) of support: Nil

Conflicting Interest: The authors declare no financial or personal relationship(s), which may have inappropriately influenced them in writing this paper.

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