Editorial

Newer oral anticoagulants and anaesthesia

Volume 2 Issue 3 - 2015

Anju Gupta,[1] Nishkarsh Gupta,[2] Rakesh Garg[2]
[1]Department of Anaesthesiology, India
[2]Department of Anaesthesiology, All India Institute of Medical Sciences, India

Correspondence: Rakesh Garg, Department of Anaesthesiology, Pain and Palliative Care, Dr BRAIRCH, All India Institute of Medical Sciences, Room No. 139, I Floor, Ansari Nagar, New Delhi–110029, India, Tel +91 9810394950; +91 9868398335, Email drrgarg@hotmail.com

Received: May 11, 2015 | **Published:** May 21, 2015

Editorial

The anaesthesiologists have to provide perioperative care including anaesthetic management to patients on anticoagulants. Anticoagulants are administered for prophylactic or therapeutic reasons. Prophylaxis is required for prevention of deep vein thrombosis, pulmonary embolism, stent thrombosis in patients with stent in situ and other thrombotic complications. The patients on anticoagulants may require elective planned surgical intervention or may be emergent/ urgent basis. Traditionally vitamin K antagonists (such as warfarin or acenocumarol), heparin (both low–molecular–weight, LMWH, and unfractionated, UFH), fondaparinux and antiplatelet agents have been used for anticoagulation and thrombo prophylaxis. The interaction of these drugs in the perioiperative period and specially for regional blocks are well studied and various recommendations exist in literature.

The conventional anticoagulants have their limitations, like unpredictable response, potential for drug–interactions and the need of parenteral administration of heparin.1 In view of these limitations and to have better drug profile, newer anticoagulants are being researched and marketed for clinical use. The newer oral anticoagulants agents (NOACs) have been developed with advantages for faster onset and offset action, better efficacy with less side effects, predictable response, reduced need of regular monitoring and less side effects.[1–5] The NOACs are direct, selective and reversible inhibitors of factor Xa (apixaban, edoxaban, rivaroxaban) or factor IIa (dabigatran). However as anaesthesiologists we must be aware of pharmacodynamics and pharmacokinetics of these newer drugs to optimise their use in the perioperative period. The experience with these newer drugs is limited and so their limited data on their management in perioperative period.

Drugs

Apixaban and Rivaroxaban are direct acting, reversible factor Xa inhibitor approved for use in stroke, systemic embolism in patients with non–valvular atrial fibrillation. Apixaban (2.5 and 5mg oral with half–life of 12hours) has 25% renal and 55% fecal elimination and should be used with caution in severe renal and hepatic impairment or associated coagulopathy.[5,6] Rivaroxaban (10mg oral) has 100% oral bioavailability and elimination half–life of 5–9 hours. It should be avoided in patients with hepatic impairment and in patients with reduced creatinine clearance.[7–9] The evidence has been reported with regards to superiority of apixaban for venous thromboembolism prophylaxis for elective knee and hip replacement surgeries, atrial fibrillation requiring chronic anticoagulation, venous thromboembolism and non–valvular atrial fibrillation.[10]

Dabigatran is a direct thrombin inhibitor and has elimination half–life is 12–17hours with 80% renal elimination.[7,8] It has been found effective for managing the patients suffering from stroke, for prevention of systemic embolization in patients with atrial fibrillation and for treatment of venous thromboembolism.[11] It may lead to gastrointestinal bleeding, dyspepsia, nausea and diarrhea.[12]

Monitoring

Monitoring the level of anticoagulation is important in the perioperative period. Various tests have been described to monitor the effects of NOACs like dilute thrombin time (hemoclot assays), activated partial thromboplastin time and ecarin clotting time for Dabigatran and antiXa assay and prothrombin time for factor Xa inhibitors (Rivaroxaban and apixaban).[13–17] These tests are not useful for assessing the degree of anticoagulation and point–of–care monitoring or rapid laboratory assays need to be developed for monitoring and titrating their effect. Monitoring of Anti–factor Xa assay, prothrombin time (PT) may be done when clinically indicated.[13] Patients on NOAC should have their renal function monitored regularly.

Concerns in perioperative period

Anaesthesiologist's needs to keep themselves updated with these drugs for better perioperative care. The concerns regarding the level of anticoagulation and thus risk haematoma formation following neuraxial blockade can be catastrophic for a patient and may cause paraplegia. Since regional blocks are being increasingly used not only for anaesthesia but also for perioperative analgesia, bleeding during vascular punctures may be concern in the patients on these newer potent anticoagulants. We need to have more evidence regarding the safety profile of these newer anticoagulants for perioperative care.[18] In a patient presenting for an emergency surgery, anaesthesiologist must anticipate the risk of bleeding during surgery and while administering neuraxial anaesthesia. Though various tests are available but there is no direct relationship with the clinical effect and an abnormal test cannot stratify the risk of bleeding. Also prophylactic administration fresh frozen plasma, platelet concentrates and factor VIIa is not routinely recommend. It will be desirable to delay for two elimination half-lives of anticoagulants to decrease the risk of hematoma formation.

Recently some recommendations have been made with regards to newer anticoagulants in the perioperative period.[19] This group recommended that these anticoagulants should be interrupted for 24h (about 2half lives) before scheduled surgery with low risk of bleeding

and for 5days before surgery or invasive procedures at moderate or high risk of bleeding. In patients with higher thrombosis risk bridging therapy with unfractionated heparin or low–molecular–weight heparin started 12h after the last dose of oral anticoagulants can be considered.

Most of the recent guidelines suggest that these drugs should be restarted 24–36 hours later depending on the bleeding risk during surgery. Some authors suggest restarting with NOACs with a half dose (75 mg for Dabigatran and 10 mg for Rivaroxaban), to minimise the risk of bleeding. Alternatively, low–molecular–weight heparin can be given early after surgery in cases when NOACs cannot be given when oral intake is not possible (bowel/gastric resection) or anaesthesiologist considers delay in restarting them.[19] The safety of neuraxial anaesthesia in patients treated with NOACs (catheter placement and removal) should be timed according to pharmacokinetic properties of the drug. The manipulation should be attempted when anticoagulant concentrations are expected at their lowest based on the half–lives. Also, any excessive bleeding or hematoma formation after catheter removal should be monitored vigilantly.[18,19] Rosencher.[20] has suggested that atleast two half –lives should pass before catheter removal. For haemostasis 30% to 40% of the function of coagulation factors is required and after two half–lives, the drug concentration in blood decreases to 25% of the initial.[20] Dabigatran is not recommended in patients with postoperative indwelling catheters. However it can be started 2–4hours after epidural anaesthesia and 6 hours after catheter removal. For rivaroxaban and apixaban epidural catheter should be inserted 4–6hour after the dose. These drugs can be restarted 22–30hours after epidural anaesthesia and 4–6hours after epidural catheter removal.[20,21]

The patients treated with NOACs do not have clotting factor deficiency but a clotting factor inhibitory defect. So, clotting factor replacement in form of fresh frozen plasma, recombinant factor VIIa etc may not be effective and cannot be recommended for routine use. Four factor Prothrombin complex concentrates (factor II, VII, IX, X) increase thrombin generation 42 and have shown some beneficial effects. They may be considered as potential reversal agents in patients with NOACs in future but we should be cautious due to thrombotic events in 1–3% of treated patients.[22,23]

Conclusion

The NOACs because of their advantages are now being prescribed more often to the patients and such patient will present frequently to anaesthesiologists for routine or emergency surgery in the times to come. A thorough knowledge about their pharmacokinetic, pharmacodynamics and drug interactions is thus essential for optimal perioperative care. Further studies are warranted to establish their clinical benefits and formulate guidelines for their perioperative use.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Funding

None.

References

1. Eikelboom JW, Weitz JI. New anticoagulants. *Circulation*. 2010;121(13):1523–1532.
2. Levy JH, Key NS, Azran MS. Novel oral anticoagulants:Implications in the perioperative setting. *Anesthesiology.* 2010;113(3):726–745.
3. Wittkowsky AK. Novel oral anticoagulants and their role in clinical practice. *Pharmacotherapy*. 2011;31(12):1175–1191.
4. Weitz JI, Eikelboom JW, Samama MM.New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis. 9th edn. American College of Chest Physicians Evidence–Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e120S–e151S.
5. Mavrakanas T, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. *Pharmacol Ther*. 2011;130(1):46–58.
6. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos*. 2009;37(1):74–81.
7. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor:single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol*. 2013;75(2):476–487.
8. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clin Pharmacokinet*. 2009;48(1):1–22.
9. De Caterina R, Husted S, Wallentin L, et al. New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes:ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease Position Paper. *J Am Coll Cardiol.* 2012;59(16):1413–1425.
10. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–2510.
11. Becattini C, Vedovati MC, Agnelli G. Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: a review of the literature. *Thromb Res*. 2012;129(3):392–400.
12. Garcia D, Libby E, Crowther MA.The new oral anticoagulants. *Blood*. 2010;115(1):15–20.
13. Castellone DD, Van Cott EM. Laboratory monitoring of new anticoagulants. *Am J Hematol*. 2010;85(3):185–187.
14. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol*. 2012;87(Suppl 1):S141–S145.
15. van Ryn J, Baruch L, Clemens A. Interpretation of point–of care INR results in patients treated with dabigatran. *Am J Med*. 2012;125(4):417–420.
16. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. *Blood Coagul Fibrinolysis*. 2012;23(2):138–143.
17. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor:Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103(6):1116–1127.
18. Gogarten W, Vandermeulen E, Van Aken H, et al. European Scoeity of Anaesthesiology: Regional anaesthesia and antithrombotic agents:recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2010;27(12):999–1015.
19. Sié P, Samama CM, Godier A, et al. Surgery and invasive procedures in patients on long–term treatment with direct oral anticoagulants:thrombin or factor–Xa inhibitors. Recommendations of the Working Group on Perioperative Haemostasis and the French Study Group on Thrombosis and Haemostasis. *Arch Cardiovasc Dis*. 2011;104(12):669–676.

20. Rosencher N, Bonnet MP, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery:Management strategies. *Anesthesia*. 2007;62(11):1154–1160.

21. Llau JV, Ferrandis R. New anticoagulants and regional anesthesia. *Curr Opin Anaesthesiol*. 2009;22(5):661–666.

22. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. A randomized, Placebo–Controlled, Crossover Study in healthy subjects. *Circulation*. 2011;124(14):1573–1579.

23. Dentali F, Marchesi C, Pierfranceschi MG, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta–analysis. *Thromb Haemost*. 2011;106(3):429–438.

Citation: Gupta A, Gupta N, Garg R. Newer oral anticoagulants and anaesthesia. *J Anesth Crit Care Open Access.* 2015;2(3):11–12.
DOI: 10.15406/jaccoa.2015.02.00059