European Spine Journal (2019) 28:693–695
https://doi.org/10.1007/s00586-018-5843-2

EXPERT'S COMMENT

Expert's comment concerning Grand Rounds case entitled "Retroperitoneal haematoma in a postoperative ALIF patient taking rivaroxaban for atrial fibrillation" by Deekonda P, Stokes OM, Chan D (Eur Spine J [2016]: DOI 10.1007/s00586-016-4822-8)

Anthony Todd[1]

Received: 21 November 2018 / Accepted: 24 November 2018 / Published online: 2 January 2019

This is a clear and well-constructed case report describing retroperitoneal haemorrhage in a 72-year-old man taking the oral anticoagulant, rivaroxaban, shortly after spinal surgery and a related literature review [1]. The authors describe the patient's presentation and bleeding management as well as summarise some key issues around NOACs and surgery.

Rivaroxaban directly inhibits factor Xa, a vital enzyme in the clotting pathway. Its onset of action is rapid, peaking at 2–4 h after ingestion, and with an elimination half-life of around 12 h or less, anticoagulation has generally worn off within 48–72 h of last exposure [2]. I will make some specific comments on the peri-operative management of rivaroxaban and the emergency management of major haemorrhage associated with NOACs.

Emergency management

The authors rightly point out that specific reversal agents are needed, with none available at the time of their report. It is common for guidelines on managing NOAC-associated bleeding to recommend *consideration* of general prothrombotic agents such as prothrombin complex concentrate (PCC)—as occurred in this case—or recombinant factor VIIa (rFVIIa), but no guideline unequivocally recommends them except, in some cases, in haemorrhage with imminent risk of death. Even then national guidelines take starkly contrasting views on the preferred choice of agent [3–5]. The difficulty in making firm recommendations to use these agents reflects their uncertain risk: benefit ratio given limited and conflicting evidence on their efficacy [6, 7] and some risk of dangerous thrombosis [8]. Their continuing place in guidelines as options, often with limited guidance on when to select that option, reflects physicians' desire to have something to propose in dangerous circumstances as much as it does any proven utility of the options available.

Fortunately, specific reversal agents are being developed for NOACs with idarucizumab widely licensed for the direct thrombin (factor II) inhibitor dabigatran and several agents emerging for factor Xa inhibitors like rivaroxaban; the first of these, andexanet, was approved by the US FDA this year though none are yet licensed in Europe. Some caution is still needed about the first wave of reversal agents for rivaroxaban with data emerging of significant thrombotic risk with andexanet [9], so the use of agents such as PCCs will continue to be an option for now. Nonetheless, it is almost certain that in the near future patients with serious haemorrhage on rivaroxaban will be managed with specific antidotes rather than the poorly evidenced option of a general prothrombotic agent.

Peri-operative NOAC management

The authors appropriately highlight the importance of balancing thrombotic and bleeding risks in making decisions about bridging therapy and raise a number of important points. The evidence base to guide decision-making here is sparse, and case reports like this one remain useful triggers for evidence review. However, on the issue of current guideline recommendations on post-operative reintroduction of anticoagulation I would take a slightly different view to the authors.

At institutional and national level in the UK and at national level in other English language healthcare systems,

✉ Anthony Todd
anthony.todd@nhs.net

[1] Department of Haematology, The Royal Devon and Exeter Hospital, Barrack Road, Devon, Exeter EX2 5DW, UK

guidelines uniformly recommend withholding anticoagulation up to 72 h after procedures with a high risk of major bleeding (e.g. a risk of bleeding at 48 h post-operatively of ≥ 2%), including spinal surgery. The authors suggest consideration of withholding NOACs for longer than this based on this case and a literature review indicating no previous reports of NOAC-associated retroperitoneal haemorrhage as well as cases of post-operative spinal haematoma despite timing of rivaroxaban reintroduction consistent with current guidelines.

However, for the latter the evidence cited is of only two patients, one of whom received warfarin and enoxaparin as well as rivaroxaban [10] and one who developed cervical haematoma 21 days after a lumbar procedure, which the paper's authors acknowledged was probably unrelated [11]. NOAC-associated retroperitoneal haemorrhage has been reported in the pivotal studies leading to licensing for idarucizumab, apixaban and rivaroxaban, post-marketing reporting for rivaroxaban as well as through multiple individual case reports [12–16]. The presented patient therefore experienced a type of haemorrhage known to occur spontaneously with NOACs including rivaroxaban, and the evidence cited linking guideline compliant rivaroxaban use to post-operative spinal haematoma is weak.

Unlike warfarin which typically takes many days to re-establish full anticoagulation, rivaroxaban re-establishes full anticoagulation within hours. This Grand Rounds patient was, therefore, fully anticoagulated for 6 days (3rd–9th post-operative days) before presenting with haemorrhage sufficiently rapid to enlarge by 6 cm in the space of a few hours. Rivaroxaban does not dissolve existing clots; it only prevents the formation of new ones: a bleed at this rate suggests that the haemorrhage was of acute onset and not due to rivaroxaban preventing establishment of haemostasis in the first few post-operative days. It is, therefore, not clear that deferring rivaroxaban reintroduction by one or more post-operative days would have prevented this haemorrhage.

Designations of patients as high or low thrombosis risk in peri-operative management guidelines are not based on evidence of peri-operative thrombosis risk but instead extrapolated from estimates of thrombosis risk in the non-operative, non-bleeding setting [17]. However, there is evidence that operative or haemorrhage-associated anticoagulation interruption doubles thrombosis risk above these levels [18], so, even in low-risk patients, additional days of interruption may represent small but significant additional thrombosis risk.

In my view, there is not yet a need to reconsider current guideline recommendations for peri-operative management of NOACs in a high bleeding risk surgery. Withholding anticoagulation longer than currently recommended will confer increased thrombosis risk, and the benefit of doing so is not established, so, even in low-risk patients, the balance of risks and benefits cannot currently be said to support this.

This case study raises important and commonly faced issues in routine practice. Fortunately, NOAC-associated haemorrhage management is becoming easier with the emergence of specific reversal agents, and though this Grand Rounds case may not in itself be strong evidence to withhold NOACs longer than currently recommended post-operatively, it shines a light on the limited evidence base underpinning current guidelines and is a useful prompt for re-evaluation of this topic.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

References

1. Deekonda P, Stokes OM, Chan D (2016) Retroperitoneal haematoma in a postoperative ALIF patient taking rivaroxaban for atrial fibrillation. Eur Spine J. https://doi.org/10.1007/s00586-016-4822-8
2. European Medicines Agency (2018) Xarelto 2.5 mg, Summary of product characteristics https://www.medicines.org.uk/emc/product/3410/smpc. Accessed 20 Nov 2018
3. PHARMAC, Best Practice Advocacy Centre New Zealand, New Zealand Government (2017) Guidelines for management of bleeding with dabigatran or rivaroxaban: for possible use in local management protocols. https://bpac.org.nz/2018/docs/dabigatran-rivaroxaban-bleeding-management.pdf. Accessed 20 Nov 2018
4. Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M (2013) Guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol 160(1):35–46
5. Clinical Excellence Commission (2017) Non-vitamin K antagonist oral anticoagulant (NOAC) Guidelines, Updated July 2017. Sydney, Australia
6. Sarode R, Milling TJ Jr, Refaai MA et al (2013) Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 128:1234–1243
7. Levy JH, Moore KT, Neal MD, Schneider D, Marcsisin VS, Ariyawansa J, Weitz JJ (2018) Rivaroxaban reversal with prothrombin complex concentrate or tranexamic acid in healthy volunteers. Thromb Haemost 16(1):54–64
8. Sørensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R (2011) Clinical review: prothrombin complex concentrates—evaluation of safety and thrombogenicity. Crit Care 15(1):201–209
9. Connolly SJ, Milling TJ Jr, Eikelboom JW et al (2016) Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 375(12):1131–1141. https://doi.org/10.1056/NEJMoa1607887
10. Radcliff KE, Ong A, Parvizi J, Post Z, Orozco F (2014) Rivaroxaban-induced epidural hematoma and cauda equina syndrome after total knee arthroplasty: a case report. Orthop Surg 2014(6):69–71. https://doi.org/10.1111/os.12085
11. Zaarour M, Hassan S, Thumallapally N, Dai Q (2015) Rivaroxaban-induced nontraumatic spinal subdural hematoma: an uncommon yet life-threatening complication. Case Rep Hematol. https://doi.org/10.1155/2015/275380

12. Pollack CV, Reilly PA, Eikelboom J et al (2015) Idarucizumab for dabigatran reversal. N Engl J Med 373:511–520. https://doi.org/10.1056/NEJMoa1502000
13. The EINSTEIN-PE Investigators (2012) Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 366:1287–1297. https://doi.org/10.1056/NEJMoa1113572
14. United States Food and Drug Administration (2016) Xarelto medication guide https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf. Accessed 18 Nov 2018
15. Hylek EM, Held C, Alexander JH et al (2014) Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE trial (Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation): predictors, characteristics, and clinical outcomes. J Am Coll Cardiol 63(20):2148–2150. https://doi.org/10.1016/j.jacc.2014.02.549
16. Saxena N, Parajuli S (2016) Spontaneous perinephric haematoma with newer oral anticoagulation in kidney transplant recipient. J Nephrol Renal Ther 2(1):1–2. https://doi.org/10.24966/NRT-7313/100002
17. Douketis JD, Spyropoulos AC, Spencer FA et al (2012) Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. Chest 141(2 Suppl):e326S–e350S. https://doi.org/10.1378/chest.11-2298
18. Sherwood MW, Douketis JD, Patel MR et al (2014) Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation (ROCKET AF). Circulation 129(18):1850–1859