ACS Case Reviews in Surgery
Vol. 3, No. 5

Perioperative Hemorrhage in the Setting of Prolonged Therapeutic Levels of Apixaban in Acute-on-Chronic Kidney Disease

AUTHORS:
Kranker LM[a]; Straughn AD[b]; Robinson ZS[b]; Layba CJ[cd]

CORRESPONDING AUTHOR:
Cathline J. Layba, MD
Department of Surgery Wright State Physicians
Miami Valley Hospital
30 E. Apple Street, Ste. 6258
Dayton, OH 45409
Phone: (937) 245-7200
Email: cjlayba@premierhealth.com

AUTHOR AFFILIATIONS:
a. Department of Surgery
Section of Acute and Critical Care Surgery
Washington University School of Medicine
St Louis, MO 63110

b. Department of Pharmacy
Miami Valley Hospital
Dayton, OH 45409

c. Department of Surgery
Wright State University Boonshoft School of Medicine
Dayton, OH 45324

d. Department of Surgery
Wright State Physicians,
Dayton, OH 45324

Background	Direct oral anticoagulants (DOACs) have risen in popularity for therapeutic anticoagulation due to decreased need for routine laboratory monitoring and reported decreased bleeding risk.[1,2] Apixaban (Eliquis, Bristol-Myers Squibb), in particular, has dosing adjustments for advanced age, low body weight, and/or elevated serum creatinine.[3] Guidelines have been established for anticoagulation in renal insufficiency, but data is limited regarding DOAC use in dialysis-dependent or severe CKD (chronic kidney disease) patients.[4]
Summary	We present a case of an older woman on apixaban (Eliquis, Bristol-Myers Squibb) with renal impairment who required emergent abdominal surgery. She developed life-threatening bleeding post-operatively though she had not taken apixaban in approximately one week. After being held for seven days, the measured apixaban level was 244 ng/ml, which exceeded the median peak and trough levels for a patient on steady-state therapy.[5] Despite current recommendations for holding DOACs perioperatively for 3 to 4 days based on her renal insufficiency (CrCl 15-20 ml/min) (creatinine clearance), her measured serum level suggested she was still fully anticoagulated. In this case, apixaban had been prescribed for the appropriate indication at the appropriate standard dose of 5 mg orally twice daily for atrial fibrillation stroke prevention (age 77 years, weight 87 kg, baseline serum creatinine 3.3), but had not cleared as predicted.
Conclusion	While apixaban (Eliquis, Bristol-Myers Squibb) may seem like a safer DOAC in those with renal impairment, surgeons should remain cognizant of the possible hemorrhagic complications in this patient population. Although hold times before surgery are of longer duration with impaired renal function, there is the possibility that patients may have therapeutic levels of apixaban even well after the recommended time of discontinuation of the medication.[6] Laboratory testing with specific drug levels, anti-FXa levels, or INR may be considered in patients with impaired renal function.after injury.

Key Words	Factor Xa inhibitor; direct oral anticoagulant; renal impairment; hemorrhage; anticoagulation; atrial fibrillation

DISCLOSURE STATEMENT:
The authors have no relevant financial relationships to disclose.

FUNDING/SUPPORT:
The authors have no relevant financial relationships or in-kind support to disclose.

RECEIVED: July 21, 2021
REVISION RECEIVED: October 14, 2021
ACCEPTED FOR PUBLICATION: November 1, 2021

To Cite: Kranker LM, Straughn AD, Robinson ZS, Layba CJ. Perioperative Hemorrhage in the Setting of Prolonged Therapeutic Levels of Apixaban in Acute-on-Chronic Kidney Disease. *ACS Case Reviews in Surgery.* 2021;3(5):16-19.

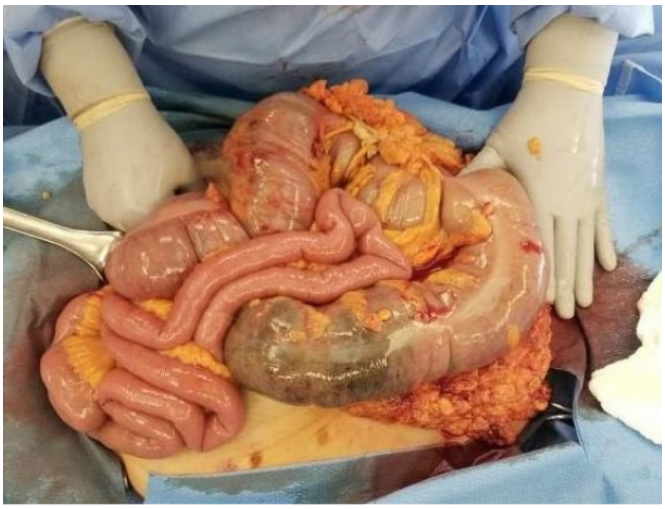
Case Description

The patient is a 77-year-old Caucasian female with comorbidities significant for diabetes, coronary artery disease (CAD), diastolic congestive heart failure (CHF), chronic kidney disease (CKD) stage IV (baseline Cr 3.3, CrCl [creatinine clearance] 15-20 ml/min), peripheral vascular disease, hypertension, hyperlipidemia, obstructive sleep apnea, obesity, prior stroke, and Parkinsonism. She was admitted a month earlier with junctional bradycardia for which a pacemaker was placed; however, she continued to have paroxysmal atrial fibrillation and was placed on apixaban (Eliquis, Bristol-Myers Squibb) 5 mg twice daily. She was re-admitted with CHF exacerbation and acute-on-chronic kidney disease (serum Cr 5.1, CrCl 7.6-13 ml/min). On admission, her apixaban was discontinued due to possible hemodialysis initiation.

She was pharmacologically diuresed, and her edema and kidney function improved with urine output returning to at least 0.5 cc/kg/hr by hospital day three; however, on hospital day six, she developed acute mental status changes with abdominal distention and emesis. Her abdomen and pelvis CT demonstrated a dilated cecum (10.2 cm) with free fluid. Significant labs included a new leukocytosis and elevated lactate; serum creatinine had improved to 3.8 from 5.1 on admission. She was started on broad-spectrum antibiotics for a presumed intra-abdominal process. Later that day, she began having large volume watery stools with rapid clinical deterioration and profound hypotension.

Given the high clinical suspicion for fulminant *Clostridium difficile* colitis the patient was taken emergently to the operating room for exploratory laparotomy. Her preoperative international normalized ratio (INR) was elevated at 3.5 despite normal liver chemistries. Citrated rapid thromboelastography was also abnormal with prolonged activated clotting time 183s (normal 89s-144s). Intra-operatively, she received fresh frozen plasma to correct her coagulopathy. Her right and transverse colon were dilated, and necrotic favoring ischemic colitis over fulminant *Clostridium difficile* colitis as the inciting event. Thus, only her right and transverse colon were resected at her index operation (Figure 1).

Figure 1. Intraoperative Photograph From First Surgery Showing Irreversible Colonic Ischemic Without Perforation (Patient's Head is Right of Photo). Published with Permission



In view of the patient's hemodynamic instability and coagulopathy, her bowel was left in discontinuity. Her abdomen was left open with a temporary abdominal closure to allow for ongoing resuscitation in the intensive care unit. Postoperatively, she continued to have sanguineous output from her temporary abdominal closure device and with elevated INR. Despite our attempts to resuscitate and correct her coagulopathy before taking her back for a second look, she continued to have ongoing hemoperitoneum and hemodynamic instability. The patient was taken back to the OR the following morning. Three liters of hemoperitoneum were evacuated, but she continued to have diffuse bleeding intraoperatively without a definitive source.

Although her DOAC was held on admission seven days prior, an apixaban level was checked and found to be 244 ng/ml, which was consistent with therapeutic anticoagulation levels. Because of these findings and concerns for ongoing bleeding, she was given four-factor prothrombin complex concentrate (4F-PCC) intraoperatively per our hospital's protocol for apixaban reversal. Though not an FDA-approved indication for use, 4F-PCC was utilized as the specific DOAC reversal agent; the FDA-approved andexanet alfa (Andexxa, Portola Pharmaceuticals) was not on our institution's formulary and has not yet been studied for perioperative anticoagulation reversal.[7] Her abdomen was re-packed and temporary closure replaced.

She remained hemodynamically stable with no further bleeding and returned to the operating room the following day for the creation of end ileostomy and fascial closure. Her *Clostridium difficile* stool test had resulted as negative prior to her final take back, and therefore, the remainder of her colon was not resected as it remained viable. Final pathology confirmed our suspected intraoperative diagnosis of ischemic colitis. She was discharged to an extended care facility on postoperative day 16.

Discussion

Since FDA approval in 2012, apixaban (Eliquis, Bristol-Myers Squibb) utilization has risen, and labeled indications have been expanded to include treatment/prophylaxis of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (AF).[1,3] For patients, the lack of routine laboratory monitoring and lower risk of bleeding make apixaban and other DOACs appealing compared to warfarin (Coumadin, Bristol-Myers Squibb).[2] While monitoring Factor Xa (FXa) inhibitors is not routinely performed, apixaban drug level testing is possible and accurate, though its availability is institution-specific.[8] Anti-FXa levels can also assess the patient's degree of anticoagulation, but this assay can be slow and is not uniformly available. In the absence of these specialized assays, several studies have shown a correlation between INR and apixaban levels; however, the INR may also be normal in patients with circulating apixaban levels (up to 50 ng/ml) and is therefore not sufficiently sensitive.[8]

Apixaban has been advocated specifically for anticoagulation in patients with chronic kidney disease, making it unique among DOACs (though randomized trials are underway).[4] The updated 2019 American Heart Association, Inc./American College of Cardiology Foundation/Heart Rhythm Society guidelines for AF treatment state it "might be reasonable" to prescribe warfarin (Coumadin, Bristol-Myers Squibb) or apixaban in patients who have end-stage CKD (CrCl <15 mL/min or dialysis requirement).[9] For stroke prevention in AF, the standard dose for apixaban is 5 mg orally twice daily. Still, a reduced dose (2.5 mg orally twice daily) is indicated for patients with at least two of the following criteria: (1) age ≥80 years, (2) weight ≤60 kg, and (3) serum creatinine ≥1.5 mg/dL.[3,5] Dialysis patients with AF are prescribed the standard dose based on pharmacokinetic data alone as randomized trials comparing apixaban to warfarin (Coumadin, Bristol-Myers Squibb) excluded dialysis patients or severe CKD (CrCr <25 mL/min).[3,4] No dosing adjustments are recommended for VTE treatment in CKD, but these studies also did not include dialysis-dependent or severe CKD patients (CrCl <15 mL/min).[3] Of note, for VTE treatment, the recent CHEST guidelines favor warfarin (Coumadin, Bristol-Myers Squibb) as the preferred anticoagulant in patients with renal disease (CrCl <30 mL/min).[10]

Patients are presumed to have therapeutic levels of anticoagulation within hours of the first dose. Apixaban primarily undergoes hepatic metabolism via several mechanisms, including demethylation, hydroxylation, and cytochrome P450 metabolism. More than half the drug (56 percent) is recovered in the feces, while 24.5 percent is recovered in the urine. The half-life of apixaban is approximately 12 hours. The pharmacokinetics of apixaban are adequately predictable, so hold times are typically trusted without verification by laboratory drug levels or anti-Xa levels. Per the FDA label, delayed elimination is not expected in mild/moderate hepatic impairment, moderate/severe renal impairment, or age greater than 65 years. The drug concentration was further increased by 17 percent in patients with renal failure after a single dose.[11] These studies providing pharmacokinetic data are generally based on one-time doses at the beginning of therapy, not in patients later in therapy at steady-state. There are case reports of grossly-delayed elimination and literature demonstrating an accumulation of apixaban in CKD.[12,13]

The predictable kinetics have led to recommended surgical hold times dependent upon the anticipated bleeding risk of the surgery and the patient's CrCl.[6] When holding anticoagulation for elective surgery in patients with normal kidney function, apixaban should typically be held for 24 hours prior to low-bleeding-risk procedures and 48 hours for moderate-to-high bleeding risk procedures.[3] For patients with CrCl less than 50 mL/min, however, the low bleeding-risk surgery hold time advocated is 34–54 hours and high bleeding-risk surgery hold time is 68 to 90 hours.[6,14]

Our patient was appropriately prescribed apixaban at the standard dose of 5 mg orally twice daily for AF stroke prevention (age 77, weight 87 kg, baseline serum creatinine 3.3). Though the surgery was not elective, apixaban had been held during her hospitalization. Before the first surgery, our patient's INR was 2.7, while receiving daily oral aspirin (Bayer) 81 mg and VTE prophylaxis with subcutaneous heparin sodium (heparin, Pfizer). When she developed life-threatening bleeding, the apixaban level measured 244 ng/mL, exceeding median peak and trough

levels for a patient on steady-state therapy.[5] With a hold time at that point of approximately seven days, she had far exceeded her recommended hold time of 3 to 4 days based on renal insufficiency (CrCl 15–20 mL/min, depending on calculation method) but was still fully anticoagulated.

Conclusion

Until a consensus is reached in the literature and more data is available on the use of apixaban (Eliquis, Bristol-Myers Squibb) and other DOACs in patients with CKD or CrCl <25 mL/min, surgeons should remain hypervigilant of the possible hemorrhagic complications in this patient population. Although hold times before surgery are of longer duration with impaired renal function, there is the possibility that patients may have therapeutic levels of apixaban even well after recommended hold times.

Lessons Learned

Evaluation of patients' renal function is imperative in DOAC choice and dosing. Hold times for DOACs should be lengthened in impaired creatinine clearance.[6] Laboratory testing with specific drug levels, anti-FXa levels, or INR may be considered in patients with impaired renal function. In the event of life-threatening bleeding in patients taking apixaban (Eliquis, Bristol-Myers Squibb), 4F-PCC or andexanet alfa (Andexxa, Portola Pharmaceuticals) may be required to establish hemostasis.[15,16]

References

1. Alcusky M, McManus DD, Hume AL, Fisher M, Tjia J, Lapane KL. Changes in Anticoagulant Utilization Among United States Nursing Home Residents With Atrial Fibrillation From 2011 to 2016. *J Am Heart Assoc*. 2019;8(9):e012023. doi:10.1161/JAHA.119.012023
2. Boom MS, Berghuis EM, Nieuwkerk PT, Pinedo S, Büller HR. When do patients prefer a direct oral anticoagulant over a vitamin K antagonist?. *Neth J Med*. 2015;73(8):368-372.
3. Apixaban. Package insert. Bristol-Myers Squibb Company; 2019.
4. Hylek EM. Apixaban for End-Stage Kidney Disease. *Circulation*. 2018;138(15):1534-1536. doi:10.1161/CIRCULATIONAHA.118.036449
5. Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. *Blood Rev*. 2017;31(1):77-84. doi:10.1016/j.blre.2016.08.006
6. Kaatz S, Mahan CE, Nakhle A, et al. Management of elective surgery and emergent bleeding with direct oral anticoagulants. *Curr Cardiol Rep*. 2017;19(12):124. Published 2017 Oct 24. doi:10.1007/s11886-017-0930-2
7. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in J Am Coll Cardiol. 2021 Jun 1;77(21):2760]. *J Am Coll Cardiol*. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053
8. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. *Chest*. 2017;151(1):127-138. doi:10.1016/j.chest.2016.08.1462
9. Writing Group Members, January CT, Wann LS, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2019;16(8):e66-e93. doi:10.1016/j.hrthm.2019.01.024
10. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in Chest. 2016 Oct;150(4):988]. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026
11. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet*. 2019;58(10):1265-1279. doi:10.1007/s40262-019-00775-z
12. Jain N, Reilly RF. Clinical pharmacology of oral anticoagulants in patients with kidney disease [published correction appears in Clin J Am Soc Nephrol. 2019 May 7;14(5):750]. *Clin J Am Soc Nephrol*. 2019;14(2):278-287. doi:10.2215/CJN.02170218
13. Robinson ZS, Harper NG. Apixaban levels detected in a patient 10 days from last known dose while experiencing acute on chronic kidney disease. *Ann Pharmacother*. 2021;55(5):687-688. doi:10.1177/1060028020962794
14. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016;41(1):206-232. doi:10.1007/s11239-015-1310-7
15. ANDEXXA, coagulation factor Xa (recombinant), inactivated-zhzo. Package insert. Portola Pharmaceuticals Inc; 2018.
16. Smith MN, Deloney L, Carter C, Weant KA, Eriksson EA. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. *J Thromb Thrombolysis*. 2019;48(2):250-255. doi:10.1007/s11239-019-01846-5