Utilization of apixaban anti-Xa levels in transition from apixaban to warfarin in a patient with chronic renal dysfunction

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Purpose. The effect of apixaban on anti–factor Xa (anti-Xa) assays and international normalized ratio (INR) complicates transitions between anticoagulant agents. When switching from apixaban to warfarin, the recommendation is to begin both a parenteral anticoagulant and warfarin at the time of the next apixaban dose and to discontinue the parenteral agent when the INR is in an acceptable range. This proves challenging in renal dysfunction, as continued presence of apixaban contributes to both a prolonged effect on the INR and continued therapeutic levels of anticoagulation.

Summary. This case describes the transition of apixaban to warfarin in a patient with acute on chronic kidney disease and recent deep vein thrombosis, utilizing chromogenic apixaban anti-Xa assays to assess the level of anticoagulation and avoid unnecessary parenteral anticoagulation.

Conclusion. Utilization of apixaban anti-Xa levels aided in the transition from apixaban to warfarin in a patient with chronic renal failure and avoided need for parenteral bridging therapy.

Keywords: anticoagulation monitoring, apixaban, warfarin, anti-Xa levels, parenteral bridging, renal dysfunction

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Apixaban is indicated for the reduction of stroke risk in nonvalvular atrial fibrillation, treatment of venous thromboembolism (VTE), and prevention of VTE in specific patient populations.[1] Dosing of apixaban ranges from 2.5 mg to 10 mg by mouth twice daily, depending on the indication and potentially renal function as well, mainly when considering patients with atrial fibrillation.

Patients with end-stage renal disease (ESRD) and patients with a serum creatinine concentration (SCr) greater than 2.5 mg/dL or creatinine clearance (CL_{cr}) less than 25 mL/min were excluded from the AMPLIFY trial.[2] The approved dosing regimen for the initial treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) is 10 mg by mouth twice daily for 7 days, followed by 5 mg twice daily for all patients with CL_{cr} greater than 25 mL/min.[3]

A benefit of apixaban over other non–direct oral anticoagulation treatment options such as warfarin, unfractionated heparin (UFH), and low-molecular-weight heparins is a need for minimal monitoring. If warranted, chromogenic apixaban anti–factor Xa (anti-Xa) assays can be obtained to quantitatively assess the apixaban drug level. These methods are yet to be approved by the Food and Drug Administration (FDA), and apixaban anti-Xa assays may not be available at all institutions. However, some pharmacokinetic and clinical outcomes data associating drug levels with degree of anticoagulation compared to standard anticoagulation assays is available.[4-13] No data from randomized controlled trials relating drug levels with efficacy and safety outcomes are available.

Apixaban exhibits an effect on many coagulation assays, including

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anti-Xa and prothrombin time (PT) assays.[9,14-17] PT is utilized to calculate international normalized ratios (INRs), which are frequently used to monitor warfarin therapy.[18] Apixaban use therefore would also impact INR results. Understanding the influence of apixaban on these assays is vital to appropriate interpretation of the results. Knowledge of an institution's instrumentation is also crucial, as the effect of apixaban on laboratory measurements varies by instrumentation.[10,19]

The effect of apixaban on anti-Xa assays and PT provides a challenge when transitioning between anticoagulant agents, especially when clearance of apixaban is delayed secondary to renal dysfunction. Clinical case series data describing the transition from apixaban to UFH in patients with renal dysfunction is available.[4]

When switching from apixaban to warfarin, the recommendation is to begin both a parenteral anticoagulant and warfarin at the time of the next apixaban dose and discontinue the parenteral agent when the INR is in an acceptable range.[1] This proves challenging in the context of renal dysfunction, as the continued presence of apixaban contributes to both a prolonged effect on the INR and continued therapeutic levels of anticoagulation. The addition of a therapeutic parenteral agent during transition of therapy would then be potentially unnecessary. This case report describes the transition from apixaban to warfarin in a patient with renal dysfunction.

KEY POINTS

- The effect of apixaban on international normalized ratio provides a challenge when transitioning to warfarin and is further complicated in patients with renal dysfunction.
- Elevated concentrations of apixaban can occur in patients with chronic kidney disease, making warfarin therapy a potentially more appropriate option.
- Chromogenic apixaban anti-Xa assays are a tool that can assist clinicians in transitioning between anticoagulants, particularly in cases involving recent venous thromboembolism.

Case report

A Caucasian, 72-year-old, 95.7-kg female was admitted for a tibial fracture secondary to a fall. Her height was 63 inches, with a body mass index of 37.4 kg/m^2. Pertinent medical history included hypertension, stage 3 chronic kidney disease (CKD), heart failure with reduced ejection fraction, ischemic cardiomyopathy, non–ST-segment elevation myocardial infarction (NSTEMI) and percutaneous coronary intervention with drug-eluting stent placement (1 month prior to admission), type 2 diabetes mellitus, hypothyroidism, obesity, anemia, and gastroesophageal reflux disease.

In addition to the admission for NSTEMI 1 month previously, the patient also had a second admission for a NSTEMI 9 days prior to the admission for a fracture described here. During her second admission, the patient was also diagnosed with an acute left proximal vein DVT and was initiated on apixaban 10 mg by mouth twice daily for 7 days and then 5 mg twice daily.

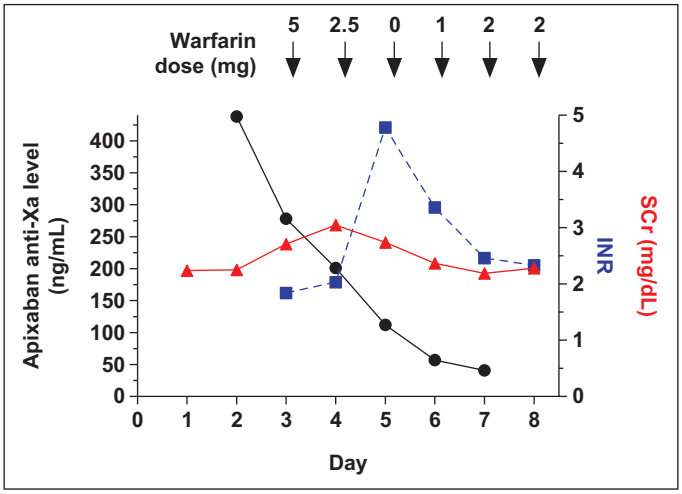
Throughout the patient's second admission, the SCr had remained at her baseline, ranging from 2.06 to 2.22 mg/dL. Her baseline INR prior to initiation of apixaban was 0.98, and liver function test results were all within normal limits. Upon readmission, for the tibial fracture, the SCr was 2.24 (CL_{cr} was 34 mL/min, as calculated using the Cockroft-Gault method with actual body weight).

Scheduled home medications prior to the admission included apixaban 10 mg twice daily, duloxetine 20 mg twice daily, ferrous sulfate 650 mg daily, gabapentin 300 mg twice daily, hydralazine 25 mg 3 times daily, insulin isophane and regular (70/30) 60 units twice daily plus insulin aspart (dosing per moderate sliding scale) with meals, isosorbide dinitrate 20 mg 3 times daily, levothyroxine 112 µg daily, metoprolol succinate 25 mg daily, olanzapine 2.5 mg daily, omeprazole 20 mg daily, rosuvastatin 20 mg daily, ticagrelor 90 mg twice daily, and torsemide 40 mg daily.

On the evening of admission, apixaban was withheld in anticipation of surgical repair of the tibial fracture the following morning. The morning of the procedure, 20 hours following the last apixaban dose, an apixaban anti-Xa assay resulted at 438 ng/mL. Plasma for this chromogenic anti-Xa assay was drawn during sampling for other morning laboratory tests, and results were obtained less than 90 minutes after collection. The clinical anticoagulation pharmacist promptly reviewed the anti-Xa level and discussed it with the surgical team 4 hours prior to the scheduled procedure. The option of giving prothrombin complex concentrate was mentioned, but the surgeon elected not to use it. The surgeon proceeded with the nailing of the intramedullary left tibia despite the elevated apixaban level, as the procedure was deemed to pose a low to intermediate bleeding risk. The estimated surgical blood loss was 50 mL. Postoperatively the surgeon deferred anticoagulation decisions to the hospitalist team. The clinical anticoagulation pharmacist also noted the poor renal function, in addition to the elevated apixaban anti-Xa level. After consultation with the hospitalist on the case, the patient was deemed to not be an ideal candidate for continued apixaban therapy. She was subsequently transitioned to warfarin with orders to start taking the medication on postoperative day 1, with a goal INR of 2 to 3.

Details of the admission and warfarin dosing are displayed in Figure 1. Since apixaban can impact INR, apixaban anti-Xa levels were also monitored. Due to the patient's recent thrombosis, which placed her at high

Figure 1. Laboratory measurements performed and warfarin doses administered during hospitalization. Laboratory results and warfarin dosing are displayed by day of hospitalization. The evening of admission is day 1. Laboratory results on day 2 and beyond were morning measurements. Warfarin is administered at 4 PM at the reporting institution. SCr indicates serum creatinine; INR, international normalized ratio.



risk for thrombosis with decreased mobility postoperatively, there was a plan to evaluate the need for parenteral bridging therapy when apixaban anti-Xa levels approached 100 ng/mL based on information found in a search of available literature.[13] The patient had many risk factors for increased warfarin sensitivity during admission, including recent fracture, renal disease, decreased oral intake, omeprazole therapy, scheduled acetaminophen use, and tramadol therapy as needed post procedure. Thromboembolic risk factors included recent surgery, trauma, immobility, and recent DVT. Hemorrhagic risk factors included a recent invasive procedure, renal disease, anemia, and concomitant ticagrelor use indicating that the patient was also at high risk for bleeding.

On postoperative day 1, the INR was 1.84, demonstrating the effect of apixaban on this value, as the baseline INR during a previous admission was 0.98. The apixaban anti-Xa level remained elevated at 278 ng/mL; a plasma sample for this assay was drawn about 24 hours after the previous level was obtained, and daily apixaban anti-Xa determinations in conjunction with morning laboratory testing was ordered. Considering the patient's recent acute thrombosis and the desire to obtain the INR goal in a timely manner, warfarin was dosed at 5 mg on the first day of therapy. This warfarin dose was given at 4 PM, which is the standard warfarin administration time at the health system. Since the patient was within 24 hours of surgery and the apixaban level was greater than 100 ng/mL, no parenteral therapy was initiated.

On postoperative day 2, the warfarin dose was halved secondary to an acute increase in the INR to 2.03 and decreased oral intake. The patient was designated as "nothing by mouth" prior to the procedure and her diet was subsequently advanced postoperatively. Significant and persistent nausea led to minimal dietary intake. Also displayed in Figure 1, the SCr increased to 2.74 on postoperative day 2 and further increased to 3.08 on postoperative day 3 before decreasing. This acute-on-chronic renal insufficiency likely delayed the clearance of apixaban even further.

The INR jumped to 4.78 on day 3 of therapy. The apixaban anti-Xa level persisted above 100 ng/mL and was likely still impacting the INR to a small degree, but warfarin sensitivity was the likely cause of the INR increase. Hemoglobin measurements were stable, and no other signs or symptoms of bleeding were noted. Warfarin was withheld.

The next day, the INR trended down adequately to 3.36, so warfarin was conservatively resumed at a dose of 1 mg. As the apixaban level was now 57 ng/mL (5 days after the last dose), the effect of apixaban on the INR was likely minimal. However, given the continued presence of apixaban and supratherapeutic INR, parenteral anticoagulation for bridging therapy was no longer considered. On postoperative day 5, a final apixaban anti-Xa assay was performed and resulted at 41 ng/mL. Warfarin was dosed at 2 mg, and the INR steeply decreased to 2.46, which was within the therapeutic range.

The downward trend in INR slowed on postoperative day 6, with an INR of 2.33, and the patient was scheduled for transfer to a short-term subacute rehabilitation facility later that day. A 2-mg warfarin dose was repeated prior to the transfer, as the patient had previously shown increased warfarin sensitivity and the full effect of the 2-mg dose from the previous day was not yet evident.

The patient was discharged, with a recommendation to tentatively target 14 mg of warfarin per week, with daily INR checks, while at the short-term subacute rehabilitation facility. Throughout her stay the INR fluctuated slightly, and the patient was discharged on a warfarin dosage of 16 mg per week.

Discussion

When transitioning from apixaban to warfarin, the FDA-approved prescribing information recommendation is to begin both a parenteral anticoagulant and warfarin at the time of the next apixaban dose and to discontinue the parenteral agent when the INR is in an acceptable range.[1] Potential issues with

the parenteral bridging approach include the need for additional education on the agent and its administration, cost, need for renal monitoring and possible dose adjustment, and potential for noncompliance associated with injections. Apixaban therapy is not recommended during the transition due to the documented impact of oral factor Xa inhibitors on INR monitoring.[15,16]

The influence of oral factor Xa inhibitors on INR is reagent and instrument specific. Diagnostica Stago instrumentation (Diagnostica Stago, Inc., Parsippany, NJ) is used for hemostasis laboratory assays at the reporting institution, including the STA-R Evolution Expert Series automated coagulation analyzer; the STA Apixaban Calibrator, STA Apixaban Control, and STA Liquid Anti-Xa reagents are utilized. The assay results are evaluated at the reporting institution approximately 90 minutes from the time of plasma collection. Pharmacokinetic data from an institution utilizing the same instrumentation indicated a median INR of 1.4 following 1 dose of apixaban (5 mg in 72.7% of patients and 2.5 mg in 27.3% of patients), with 84.5% of patients exhibiting an elevation in INR.[16]

This patient's baseline INR was 0.98 prior to initiation of apixaban and 1.84 prior to the first dose of warfarin, values that were above the median value reported in the previously mentioned study but within the observed range.[16] It is evident the presence of apixaban impacted this patient's INR. This distinct increase in INR caused by apixaban makes using apixaban as a bridge to warfarin therapy challenging, as it is impossible to tell how much of the INR elevation is due to apixaban versus warfarin.

Guidance on how to utilize oral therapy, like apixaban, to transition to warfarin if parenteral therapy is not an option has recently become available.[20] Burnett et al[20] described an option to overlap either rivaroxaban or apixaban therapy with warfarin therapy until the INR is in the goal range, with the INR measured right before the dose of the factor Xa inhibitor. The factor Xa inhibitor would be at trough levels at this time and have the lowest impact on INR; however, the timing of these INR determinations could be challenging. For example, apixaban is dosed twice daily, and a majority of clinics operate from 8:00 AM to 5:00 PM, making it difficult to obtain this laboratory value if a patient is unavailable prior to the morning dose. This strategy did not apply in the case described here, as the patient was not receiving apixaban and warfarin concomitantly and only exhibited delayed clearance of apixaban.

Prolonged clearance of apixaban can occur in patients with CKD despite the drug being the least renally excreted direct oral anticoagulant.[21] Pharmacokinetic data has shown a mean area under the curve increase of 16% to 38% in patients with CKD, with higher percentages seen in patients with higher degrees of renal impairment.[22] Apixaban is not contraindicated in this patient population, but noted accumulation of the drug can occur, making warfarin therapy a potentially more appropriate option.[21,22]

While use of apixaban anti-Xa levels to guide apixaban dosing is not an FDA-approved method and changing the dose of apixaban based on anti-Xa levels is not supported by literature, these levels can be useful in certain situations. Byon et al[13] described anti-Xa levels in patients taking apixaban 10 mg twice daily for venous thromboembolism. The median trough concentration was 120.2 ng/mL, with a 5th to 95th percentile range of 41.1 to 334.5 ng/mL. Data on patients taking apixaban 5 mg twice daily for venous thromboembolism indicated a predicted median trough concentration of 63.2 ng/mL, with a 5th to 95th percentile range of 21.7 to 176.5 ng/mL.

The apixaban-treated patient described here was transitioned from 10 mg twice daily to 5 mg twice daily dosing on the day of admission. A 20-hour postdose apixaban level was 438 ng/mL, well over the expected trough range for either dosing regimen, and the patient exhibited a significant delay in the clearance of apixaban and was potentially overanticoagulated despite no signs or symptoms of bleeding.[13]

Evaluating subsequent apixaban anti-Xa levels of 278 ng/mL on day 3 of hospitalization and 201 ng/mL on day 4, we determined that the exhibited half-life of apixaban in this patient was prolonged relative to the expected apixaban half-life of 8 to 15 hours.[23] The patient's renal function was acutely changing throughout the admission and not at steady state, so an exact half-life is difficult to calculate. Daily apixaban anti-Xa levels were obtained in conjunction with morning laboratory testing due to the patient's variable renal function, a desire to assess the potential impact on the INR result, and as a quantitative measurement to determine when to potentially initiate parenteral bridging therapy.

A recent history of a DVT would normally have made this patient a candidate for parenteral bridging.[24,25] In this case, the presence of apixaban negated the need for parenteral bridging. Bridging would have been started when the apixaban level approached 100 ng/mL, as the anticoagulation effect of apixaban is decreased when levels drop below this value and is almost nonexistent at levels less than 50 ng/mL.[11,12] The 100-ng/mL threshold would have typically been chosen in this case due to the need for therapeutic anticoagulation for the recent acute DVT. Bridging was not indicated for this patient because the apixaban levels remained above 100 ng/mL for several days. Once the apixaban level was below 100 ng/mL, the patient's INR was supratherapeutic, precluding the need for parenteral bridging. Bridging therapy was also not indicated within 24 hours of the patient's procedure.[24,25] Discontinuation of the apixaban level monitoring could have been considered following the 57-ng/mL level, the first level below 100 ng/mL. One additional level was obtained, as the INR had not yet stabilized.

Testing for apixaban anti-Xa levels is not readily available at all institutions. While use of activated partial thromboplastin time (aPTT) and

heparin anti-Xa levels may be useful in transitioning patients from apixaban to unfractionated heparin,[14] these assays provide only a qualitative measure of apixaban and are not used in warfarin monitoring.[10] As a result, their utility in transitioning from apixaban to warfarin is limited.

Overlap of apixaban therapy with warfarin therapy was utilized in this case. Normally, parenteral bridging therapy would be indicated when transitioning from apixaban to warfarin in the setting of recent thrombosis. However, delayed apixaban clearance secondary to CKD allowed for therapeutic transition to warfarin without parenteral therapy. This transition strategy is not indicated in every patient scenario. It may be reasonable to forego parenteral bridging therapy in patients with low thrombosis risk (ie, historical DVT many years ago and a, low CHA_2DS_2-VASC score).[25,26] Alternatively, bridging therapy could be delayed until the apixaban levels drop below 50 ng/mL, for low-thrombosis-risk patients, or for patients at high risk for bleeding. In the case presented here, the patient had a high thrombosis and high bleeding risk. Beginning parenteral bridging as stated in the FDA-approved prescribing information may have led to overanticoagulation and an increased risk of bleeding.

This case highlights the difficult transition from apixaban to warfarin in a patient with renal dysfunction, including delayed clearance of apixaban and subsequently a prolonged effect of apixaban on the INR. Without the monitoring of apixaban anti-Xa levels, INR interpretation would have been difficult. Additionally, the patient may have been inappropriately started on parenteral anticoagulation for bridging therapy if the INR was subtherapeutic. This would have led to overanticoagulation and increased bleeding risk. Although the presence of apixaban proved challenging in the interpretation of the INR, utilization of apixaban anti-Xa levels to determine a quantitative presence of apixaban aided in the safe transition to warfarin therapy for treatment of a recent acute DVT.

Conclusion

Utilization of apixaban anti-Xa levels aided in the transition from apixaban to warfarin in a patient with chronic renal failure and avoided the need for parenteral bridging therapy.

Disclosures

The authors have declared no potential conflicts of interest.

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