Original Work

Concurrent Reversal of Apixaban and Dabigatran for Emergent Surgery and the Impact of a Therapeutic Interchange: A Case Report

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Over the last 10 years, the number of anticoagulation options has greatly expanded. Traditional anticoagulant therapies, once considered the standard of care, now are challenged by new classes of drugs including direct factor Xa inhibitors, indirect factor Xa inhibitors, and direct thrombin inhibitors. Since first being introduced in 2010, agents including dabigatran, rivaroxaban, apixaban, and edoxaban have seen an exponential rise in use, which has been attributed to patient ease of use, increasing clinical efficacy data, and limited clinical monitoring requirements compared to traditional therapy. These agents (often termed direct oral anticoagulants or DOACs) offer patients and clinicians an injection-free treatment option for common conditions such as atrial fibrillation, venous thromboembolism, pulmonary embolism, and thromboprophylaxis. Recently, the American College of Chest Physicians (CHEST) guidelines adopted DOACs as a first-line antithrombotic treatment option for patients with certain cardiac conditions, such as atrial fibrillation.[1] However, increased usage of the DOACs has introduced an increased level of complexity when seeking anticoagulation reversal. Appropriate reversal is often critical in achieving safe patient outcomes during acute injuries and during procedures in which blood loss may occur. The following case report discusses a unique situation in which a transferred patient needing emergent anticoagulant reversal received two different DOAC agents as result of an outside hospital therapeutic interchange.

Background

An important consideration pertaining to all anticoagulants is understanding reversal strategies to minimize blood loss. Many traditional agents utilize drug-specific reversal agents, such as phytonadione for warfarin or protamine for unfractionated heparin; however, DOAC reversal is not always as simple. In order to better understand DOAC reversal, it is helpful to understand their pharmacodynamic and pharmacokinetic characteristics.

The two main classes of the DOACs include the direct thrombin inhibitors (DTIs) and the direct factor Xa inhibitors. The only oral anticoagulant agent belonging to the DTI class is dabigatran. Dabigatran acts by directly inhibiting thrombin (factor IIa), thus preventing fibrinogen conversion to fibrin.[2] The half-life of dabigatran is estimated as 13 hours in patients with normal renal function and 18 hours in those with moderate renal impairment (creatinine clearance 30-49 mL/min).[3] For this reason, it is generally recommended to hold the medication for at least two days for patients with good renal function (creatinine clearance ≥ 80 mL/min) or for at least four days for patients with moderate renal impairment who are undergoing a planned procedure with an uncertain, intermediate, or high bleed risk when there are no increased patient bleed risk factors.[4] For patients who are unable to hold their doses of dabigatran prior to procedures, the reversal agent idarucizumab is utilized. Idarucizumab binds to dabigatran's molecular structure with such high specific affinity that it effectively prevents dabigatran from having an effect on thrombin.[5]

The other subset in the DOAC class is the direct factor Xa inhibitors: rivaroxaban, apixaban, betrixaban, and edoxaban. This class of medications works, as its name implies, through factor Xa inhibition, which prevents the conversion of prothrombin to thrombin and thus prevents fibrin clot formation downstream. The half-life for these medications varies depending on the specific agent, but on average ranges between 5-12 hours.[6] The specific Xa inhibitor focused on throughout this article is apixaban because it was the agent administered during this patient case. Depending on the patient and the type of procedure, it is generally recommended to hold apixaban doses for one to two days prior to planned procedures.[4,7] One of the most popular reversal strategies for apixaban includes prothrombin complex concentrate (PCC), which works by increasing the amount of available clotting factors for coagulation.[8] Reversal of apixaban via andexanet alfa, a new apixaban-reversal agent, was not considered in this case because it was not available at the hospital during the time of this patient case.

Patient Case

The patient of discussion is a 79-year-old female with pertinent past medical history of atrial fibrillation, who initially presented as a transfer from an outside hospital with abdominal pain and concern for cecal volvulus (see Table 1 for abbreviated timeline of events). During the patient's short admission at an outside hospital, imaging was completed which showed the severity of her medical

condition. She ultimately needed to be transferred to a facility equipped to provide a higher level of care. Hospital imaging showed a cecal volvulus measuring 10.8 cm in diameter leading to secondary small bowel obstruction. After a short evaluation at University of Wisconsin (UW) Health, the decision for urgent surgical detorsion and cecal resection was ordered by the attending physician. Given the high bleeding risk of the procedure, orders were placed to reverse the patient's anticoagulated status. Initially, Kcentra® (a type of PCC on UW Health's formulary) was ordered for the reversal of the apixaban dose administered at the outside facility. Upon UW Health pharmacist medication reconciliation, it was discovered that the patient was not on apixaban previously, but rather takes maintenance dabigatran for atrial fibrillation clotting prevention. Further investigation revealed that during the outside hospital's brief admission, a therapeutic interchange was completed exchanging the patient's daily dabigatran dose to apixaban. Further complicating the clinical situation, lab results from UW Health's emergency department indicated the patient was presenting with an acute kidney injury. Although the last administration of dabigatran was estimated to be 17 hours prior to presentation, it was decided that both apixaban and dabigatran reversal must be considered given the patient's renal status and dabigatran's pharmacokinetic profile.

The pharmacist's evaluation of reversal options supported the original order for apixaban anticoagulation reversal with PCC, which was administered at 05:48 at a dose of 25 units per kilogram. However, given PCC's limited efficacy in dabigatran reversal, the patient's limited renal clearance, and the significant surgical bleeding risk, the patient was evaluated for candidacy for idarucizumab administration. As part of the peri-procedural evaluation of dabigatran's anticoagulant effect, a thrombin time (TT) is often drawn to evaluate if the patient has any active anticoagulation attributable to dabigatran. Per UW Health protocol, a TT should be drawn on patients who may be eligible for dabigatran reversal with idarucizumab prior to its administration. Unfortunately, given the urgent nature of the patient's surgery and limited lab resources at the time of patient presentation, a TT was unable to be run quickly enough to confirm the patient's dabigatran status prior to surgery. To decrease the patient's bleeding risk, the decision was made to administer 5 grams of idarucizumab at 06:16 to reverse any lingering dabigatran anticoagulation.

TABLE 1. Timeline of Patient Case Events

Date	Time	Key Event
Day 0	10:00	Prior-to-admission dabigatran administration
	17:50	Outside hospital admission
	21:53	Apixaban 5 mg administered at outside hospital
Day 1	01:10	Discharged from outside hospital
	02:47	UW Health emergency department arrival
	05:48	PCC administered (2160 units)
	06:16	Idarucizumab administered
	07:17	Patient transfer to operating room
	14:45	Patient transfer out of post anesthesia care unit
Day 12	10:00	Discharge from hospital

Results

The patient ultimately received PCC for apixaban reversal and idarucizumab for dabigatran reversal. Surgery began at 07:17 and was completed approximately 3 hours later at 10:36. The surgery was ultimately deemed an anticoagulant reversal success with the patient only losing an estimated 50 mL of blood while in the operating room. Postoperatively, the patient was transferred to the procedural acute care unit for low systolic pressures but suffered no acute complications of the procedure.

Discussion

Based on the timing of the administration of apixaban and dabigatran relative to the start of the emergent surgery, both agents needed to be accounted for with a reversal agent. The patient in this case also presented with an acute kidney injury, which suggests she likely had increased anticoagulant serum levels due to inefficient clearance.

Since the introduction of oral Xa inhibitors, PCC has been the reversal agent of choice for patients needing rapid reversal of their anticoagulation effects. Options include 4-factor inactivated PCC (4F-PCC), 4-factor activated PCC (4F-aPCC), and 3-factor PCC. The 2018 American Society of Hematology Guidelines recommend using a 4-factor PCC (depending on the timing of the last dose) in addition to holding apixaban for patients with life-threatening bleeding.[9] In addition to the national guidelines, internal hospital guidelines for emergent reversal of apixaban state that 4F-PCC (i.e., Kcentra®) may be considered at a dose of 25-50 units/kg (max 5000 units) for emergent surgeries. Because the patient in this case received apixaban roughly 8 hours prior to surgery, PCC was given to reverse apixaban's effects at an appropriate dose of 25 units/kg.

Prior to 2015 when idarucizumab was introduced to the market, little evidence existed around the reversal of dabigatran. PCC was generally the treatment of choice despite minimal clinical evidence in humans. A 2019 study comparing the efficacy of dabigatran reversal of idarucizumab versus non-specific procoagulant therapies in vitro indicated idarucizumab was much more

efficacious than non-specific procoagulant concentrates and PCC.[10] During its phase 3 trial, idarucizumab rapidly and safely reversed the anticoagulant effects of dabigatran, and a reported 93.4% of patients had normal hemostasis intraoperatively following administration of idarucizumab.[11] At the national level, current American Society of Hematology guidelines suggest using idarucizumab for life-threatening bleeding for patients on dabigatran.[12] Given the quality of evidence for idarucizumab, it has been UW Health's option of choice for emergent surgery with patients taking dabigatran. UW Health's protocol recommends first holding dabigatran and then assessing the necessity of idarucizumab for reversal. If the last dose of dabigatran was given within 12 hours, or if it was given longer than 12 hours ago and the TT test comes back at 25 seconds or greater, idarucizumab administration is warranted. If the last dose was given greater than 12 hours and the TT test result is under 25 seconds, no reversal agent is necessary. In this case, the dabigatran was given roughly 20 hours prior to surgery, but a TT test was unable to be conducted due to overnight laboratory resources. Ultimately, idarucizumab was administered, given that the healthcare team could not confirm that there was no dabigatran activity via the TT test.

It is important that healthcare providers are aware of therapeutic interchanges that may occur at outside hospitals; these therapeutic interchanges may impact the care a patient receives, their cost of care, and potentially safety and efficacy outcomes. Due to a therapeutic interchange (i.e., using apixaban instead of dabigatran in this case), this patient needed dual reversal. Although the patient had an overall positive outcome, treatment cost was dramatically increased. The approximate cost to the patient for PCC and for idarucizumab was $11,000 each ($22,000 total). This shows that if the patient was not given apixaban at the outside hospital, PCC would not have been indicated and could have prevented an additional $11,000 cost to the patient. Patient safety is always the number one priority as healthcare practitioners, but it is important that hospitals consider the impact of using therapeutic interchanges when it comes to future treatment outcomes and costs.

Conclusion

This patient case provides a scenario in which two different DOAC medications (dabigatran and apixaban) needed to be reversed due to the patient requiring an emergent surgery with a high bleed risk. Given the limited coagulation testing data available and limited agent clearance due to kidney dysfunction, the decision was made to give both idarucizumab and PCC. This example shows how therapeutic interchanges can drastically complicate the clinical picture for patients who are transferred from one institution to another. Also, this case highlights the importance of the pharmacist medication reconciliation process given the multitude of safety concerns that are implicated if hospitals receiving transferred patients are not aware of potential interchanges that occurred to a patient's home medications. Ultimately, it is important that hospital practitioners consider the impact of therapeutic interchanges before what appears to be a simple substitution.

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