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ORIGINAL ARTICLE

Improving Patient Safety Through Proper Ordering and Administration of Andexanet Alfa

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Abstract

Objective: To evaluate prescribing practices for the anti-Xa reversal agent, andexanet alfa, to identify challenges in ordering and administering this medication, and to offer recommendations to improve patient safety.

Patients and Methods: This retrospective study reviewed all adult patients treated with andexanet alfa (AA) at a single institution between January 1, 2018, and March 31, 2020. We identified ordering and administration benchmarks based on recommendations from previous clinical trials on AA. We then reviewed these medical records to determine compliance with these benchmarks. We also collected data related to thrombotic complications and mortality.

Results: Twenty-two AA dosing sets (loading and infusion dose) were given to 20 patients. Eight (36%) dosing sets met our ordering benchmarks regarding appropriate dose, time since last direct oral anticoagulants, urgency of administration, and documentation. Three (14%) dosing sets met the administrative benchmarks of being started within 30 minutes of the initial order, and 13 (59%) dosing sets had timely infusion of the infusion dose after the loading dose. No dosing set met all our administration benchmarks. There was 1 thrombotic event within 24 hours of the correct AA dose and 1 potential death related to AA.

Conclusion: This study highlights challenges in ordering and administering AA at our institution and brings awareness to potential similar concerns at other institutions. These challenges also identified the need for optimized order sets, a streamlined administration process, and frequent provider education to improve patient safety.

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Direct oral anticoagulants (DOACs), specifically factor Xa inhibitors (eg, apixaban, rivaroxaban, and edoxaban), as well as direct thrombin inhibitors (dabigatran), are commonly used for the prevention and treatment of thromboembolism.[1-5] They represent a convenient substitution for the historically predominantly prescribed vitamin K antagonists as they allow for simpler perioperative management and bear a lower overall risk of major bleeding.[6,7] Until recently, the absence of an effective factor Xa—inhibitor reversal agent has been a significant downside of DOACs. In May 2018, the US Food and Drug Administration (FDA) approved andexanet alfa (AA), a modified recombinant factor Xa designed to reduce factor Xa—inhibitor activity by binding and sequestering it rapidly.[8,9] Andexanet alfa has been explicitly approved for the reversal of apixaban or rivaroxaban during life-threatening or uncontrolled bleeding episodes.[10]

There are 2 approved dosing regimens for AA: high dose and low dose, both consisting of an initial intravenous loading dose followed within 2 minutes by an intravenous infusion for up to 120 minutes. The selection between high-dose vs low-dose regimen depends on the patient's DOAC type, dose, and timing from the last dose.[10] Several research groups have examined the efficacy and safety of AA during episodes of bleeding.[11-13] For example, the ANNEXA-4 study found effective hemostasis in 82% (204 of 249 patients), thrombotic event in 10%, and death in 14% of

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patients included.[11] These percentages were congruent with other clinical trial reports in the literature.[14] However, outcome studies of real-world utilization report significantly higher morbidity and mortality rates.[12,15,16] It is important to note that AA is a high-risk medication that should be prescribed cautiously.

This study aimed to provide a granular review of AA-prescribing practices at a single institution and identify challenges associated with ordering and administering the drug correctly. We also aimed to identify areas for improvement and provide practical recommendations and clinical guidance to ensure better patient safety.

PATIENTS AND METHODS

Study Design

We conducted a retrospective review of all patients aged 18 years or older at the Mayo Clinic Florida campus who received AA between January 1, 2018, and March 31, 2020. Based on the ANNEXA-4 study[11], we created ordering and administration benchmarks and subsequently asked questions to guide our data collection. These benchmarks are as follows:

1. Ordering questions/benchmarks:
   - Was AA given for an FDA-approved indication?
   - Was the correct dose of AA ordered?
   - Was the last DOAC dose within 18 hours before ordering AA?
   - Was AA ordered with "STAT" priority?
   - Was the indication for AA documented?
2. Administration questions/benchmarks:
   - Was AA given within 30 minutes of ordering?
     - Did the pharmacy dispense AA within 15 minutes?
     - Was AA administered within 15 minutes of the pharmacy dispensing the medication?
   - Was the time between the AA loading and infusion dose within 10 minutes?

We then collected and critically analyzed granular data to assess our institution's adherence to these benchmarks. In addition, we assessed thrombotic and mortality rates—a possible dreaded side effect of AA. Assessed thrombotic events included venous thromboembolism and arterial thromboembolism including myocardial infarction and ischemic cerebral infarcts. Absolute counts and percentages are provided to describe results.

RESULTS

Ordering Characteristics

Twenty patients received 22 dosing sets of AA. Each dosing set of AA included both a loading dose and an infusion dose. Of the 22 dosing sets, there were 43 orders (22 loading doses and 21 infusions doses). One dosing set had a loading dose ordered without a corresponding infusion dose. Apixaban and rivaroxaban were the DOAC types used by 12 (60%) and 8 (40%) patients, respectively, and were indicated for atrial fibrillation (13 patients, 65%) or prevention or treatment of venous thromboembolism (7 patients, 35%) (Table 1).

Indications for AA were mostly bleeding 17 (77%), and the remaining 5 (23%) were given for preoperative anticoagulation reversal (Table 2). AA was ordered with STAT priority for 19 dosing sets (86%). Both the loading dose and infusion dose received a STAT designation in these dosing sets. Two dosing sets had a "routine" priority for the loading dose order and a STAT priority for the infusions dose order. Both dosing sets occurred in

TABLE 1. Patient Characteristics

Characteristic (n=20)	Value
Sex, n (%)	
Male	14 (70)
Female	6 (30)
Age (y), median (range)	74.5 (57-99)
Dosing sets (loading + infusion)	22
Orders	42
Loading doses	22
Infusion doses	21 (one not ordered)
DOAC type, n (%)	
Eliquis	12 (60)
Xarelto	8 (40)
DOAC Indication, n (%)	
Bleeding	13 (65)
Preoperative	7 (35)

DOAC, direct oral anticoagulant.

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TABLE 2. Andexanet Alfa Indication

	n=22, n (%)
Intracranial hemorrhage	11 (50)
Preoperative DOAC reversal	5 (23)
Other bleeding site	4 (18)
Gastrointestinal bleeding	2 (9)

DOAC, direct oral anticoagulant.

TABLE 3. Ordering Provider Characteristics

Characteristic	n=25, n (%)
Provider education	
Attending	7 (28)
PharmD	7 (28)
MD/DO fellow	4 (16)
APRN	3 (12)
MD/DO resident	2 (8)
RN	2 (8)
Provider specialty	
Critical care medicine	7 (28)
Emergency medicine	6 (24)
Cardiology	4 (16)
Neurology	2 (8)
Internal medicine	2 (8)
Neurosurgery	1 (4)
Heart transplant	1 (4)
Vascular surgery	1 (4)
Anesthesia	1 (4)

patients with active bleeding, one with an intracranial hemorrhage and other with gastrointestinal bleeding. The third dosing set with a routine priority involved a loading dose ordered without an infusion dose in a patient needing preoperative reversal of a DOAC. No clear explanation as to why these doses were ordered with a routine priority was found. The average time from order placement to start of AA administration was 61 minutes for the 3 doses with a routine priority and 59 minutes for the 19 doses with a STAT priority. Five dosing sets (23 %) were ordered more than 18 hours after the last DOAC dose. Two dosing sets (9%) were ordered more than 30 hours after the last DOAC dose. Of the 22 dosing sets, 2 sets (9%) did not have accompanying documentation as to why the medication was ordered. Three of the dosing sets had a different ordering provider for the loading dose and for the infusion dose. These results revealed 25 unique ordering providers with 6 different educational backgrounds and from 9 different subspecialties (Table 3). Seventeen providers (68%) used one of the 2 predefined order sets to order AA, whereas the remaining 8 (32%) ordered the medication through individual orders.

The dosing regimen selection (high vs low dose) was appropriate in 15 dosing sets (68%), whereas for 7 dosing sets (32%), the dose was chosen incorrectly. The most common mistake, which occurred with 6 dosing sets (27%), was ordering a high-dose or low-dose regimen when the opposite regimen was indicated. The seventh incorrect dosing set involved a nonstandard loading dose ordered without an infusion dose. One of the 7 cases acknowledged that the high dose was ordered incorrectly, whereas the remaining 6 cases did not appear to have any documentation regarding why providers selected an alternative dosing regimen. Furthermore, only 18 dosing sets (82%) had the correct loading and infusion doses ordered together. In summary, AA was correctly ordered in 8 (36%) dosing sets—meaning that both dosing regimen (high vs low dose) and loading/infusion dose combination were selected appropriately, that the medication was ordered STAT, and that the patient's last DOAC dose was within 18 hours of the order placement.

Administration Characteristics

Various aspects of the 43 medication administrations, including loading and infusion doses, are demonstrated in Table 4. The loading dose for 3 order sets (14%) was started within 30 minutes of order placement. Eight order sets (36%) were started more than 60 minutes after order placement (range, 63-148 minutes). This 30-minute window was broken down to include 15 minutes for the pharmacy to dispense the medication and have it ready for the nursing staff and then 15 minutes for the nursing staff to start administering the loading dose. The pharmacy dispensing time was under 15 minutes for 4 order sets (18%). Once the medication was released from the pharmacy, 11 of the 22 order sets (50%) took longer than 15 minutes to be started.

TABLE 4. Administration Times

	n=22, n (%)
Time from order to administration (min)	
≤30	3 (14)
>30 (31-148)	19 (86)
Pharmacy dispense time (min)	
≤15	4 (18)
>15 (24-72)	18 (82)
Dispense time to administration (min)	
0-15	11 (50)
16-30	4 (18)
31-60	5 (23)
>60 (108-121)	2 (9)
Loading to infusion dose (min)	
0-2	4 (18)
3-10	9 (41)
11-20	5 (23)
20-30	1 (4.5)
>30 (170)	1 (4.5)
NA	2 (9%)

Finally, the interval between the loading dose and the start of the infusion dose was assessed. Of the 22 order sets, only 20 had a loading and infusion dose given. One order set did not have a correlating infusion dose ordered, while a second set had it ordered, but it was not given for an unclear reason. Of the 20 completed order sets, 16 (80%) had a loading to infusion dose time longer than 2 minutes, and 7 (35%) had a time longer than 10 minutes. The longest recorded loading to infusion time was 170 minutes in 1 patient. In summary, no dosing set met all administration benchmarks of being given within 30 minutes of order placement and with a maximum loading to infusion dose time of 10 minutes.

Thrombotic Complications and Mortality

In our cohort, they were 5 thrombotic events (25%) and 7 fatalities (35%) (Table 5). Of the 7 fatalities, 2 did not have thrombotic complications and died from intracranial hemorrhage (patients 6 and 7). The remaining 5 fatalities had thrombotic complications. Among these 5 patients, 3 developed multifocal ischemic infarcts in the setting atrial fibrillation off anticoagulation (patients 1-3). One of these 3 infarcts (patient 3) occurred within 24 hours of AA, while the remaining 2 occurred on day 3 after AA. Patient 4 with metastatic lung cancer developed a pulmonary embolism on day 19 after AA. Finally, patient 5, who required preoperative DOAC reversal for bowel surgery, developed a massive pulmonary embolism and mesenteric vein thrombosis within 24 hours of a higher-than-expected AA loading dose and no subsequent infusion dose.

DISCUSSION

Prescription of medications used to reverse DOACs, such as AA, warrants particular caution as the associated risks of thrombotic complications and death reported in the literature span from 0% to 31% and 10% to 35%, respectively.[11,12,14,15,17,18] Along with these risks, there is also a significant cost to AA, with a median projected cost of $22,120/patient compared with $5670/patient for 4-factor prothrombin complex concentrate (4F-PCC) that consists of coagulations factors II, VII, IX, and X.[19] Therefore, it is imperative that such a costly and potentially harmful medication be ordered and administered appropriately. To our knowledge, this study is the first of its kind to granularly illuminate the challenges and gaps in how AA is ordered and administered.

Our study found differences in order practices among the 25 providers who ordered AA. As expected, AA was prescribed for bleeding in most patients, and intracranial hemorrhage was the most common site of bleeding. A smaller number of patients received AA as an off-label use for preoperative anticoagulation reversal. Of note, our study did not evaluate the severity of bleeding or the urgency of surgery. Not all orders in our study were ordered with STAT priority. The average time from order to administration was similar for STAT (59 min, n = 19) and routine (61 minutes, n = 3) orders. Despite low patient numbers, our sample did not suggest that ordering a medication STAT decreased the time to administration and ordering a medication routine did not prolong time to administration.

Almost 25% of the dosing sets were ordered more than 18 hours after the last DOAC dose. The 18-hour time window benchmark stems from the ANNEXA-4 study.[11] The efficacy of AA beyond this time window is unclear. No documentation was found as to why AA was ordered outside this

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TABLE 5. Thrombosis and Mortality

n	Age, gender	DOAC indication	DOAC	Minimum time since DOAC (h)	AA dose (loading, infusion)	Reason for reversal	Thrombotic event	Cause of death
1	85-y-old female	AFIB	Rivaroxaban 20 mg daily	10	Low	Intracranial hemorrhage	Multifocal stroke on day 3 after AA	Intracranial hemorrhage on day 9
2	80-y-old male	AFIB	Rivaroxaban (dose unknown)	16.5	High	Intracranial hemorrhage	Multifocal stroke on day 3 after AA	Intracranial hemorrhage on day 27
3	99-y-old female	AFIB	Apixaban 5 mg twice daily	33	Low	Muscular hematoma	Multifocal stroke within 24 h of AA	Found unresponsive 9 d after AA
4	74-y-old male	AFIB	Apixaban 5 mg twice daily	28	Low	Intracranial hemorrhage	PE on day 19 after AA	Metastatic lung cancer and pneumonia on day 40
5	63-y-old male	DVT	Apixaban 5 mg twice daily	3	High dose infusion without loading dose	Preoperative for incarcerated ventral hernia	Same-day postoperative ischemic bowel, back to OR, and intraoperative PE and mesenteric DVT	Massive PE and bowel ischemia on day 1
6	80-y-old male	AFIB	Apixaban 2.5 mg twice daily	<7	Low dose	Intracranial hemorrhage	NA	Intracranial hemorrhage on day 9
7	72-y-old male	DVT	Apixaban 5 mg twice daily	12	Low dose	Intracranial hemorrhage	NA	Intracranial hemorrhage on day 1

AA, andexanet alfa; AFIB, atrial fibrillation; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; NA, not available; OR, operating room; PE, pulmonary embolism.

18-hour time window. Our results also show high rates of selecting an inaccurate dosing regimen (high vs low dose) and inconsistent dosing combinations for the loading and infusion doses. These variances are explainable as multiple components of the patient's history (timing, dose, and type of DOAC) must be considered in the ordering process, and not all providers are educated on how to order this medication correctly. Another important note is that 2 AA dosing sets (9%) did not have accompanying documentation as to why the medicine was ordered. The only documentation of administration was the initial order showing who ordered the medication, pharmacy dispensing, and nursing administration time. In our view, there should always be documentation for high-risk and expensive medication. Incomplete or inadequate documentation leaves ample room for error[20] and opens the possibility of legal liability.

These variations in practice are believed to be at least partially because of the ability of any provider to order AA, despite their familiarity or lack thereof with the drug. As reported, 25 different providers with 6 different education levels across 9 specialties ordered AA. Furthermore, the frequent turnover of trainees and advanced practice providers highlights the need for ongoing education to minimize the risk of errors. We suggest using a single-optimized order set in the electronic medical record to tackle these challenges. This order set can streamline the ordering process, provide education on ordering the medication, and ensure accurate dosing by forcing providers to obtain the relevant history and then automatically selecting the correct dosing regimen and dose. All orders would default to STAT priority. We also recommend removing individual orders for the medication so that ordering always creates a dosing set with a loading dose and infusion dose. If an error is made when ordering one of these components, the entire dosing set must be discontinued and reentered. Finally, the order set would require an indication for AA, thus providing sufficient documentation. Another recommendation to potentially decrease ordering errors is to have an oversight committee trained in ordering AA. This committee would have an on-call provider or pharmacist to review and discuss all AA orders with ordering providers before or immediately after order placement. Such a committee can ensure that AA is ordered for an appropriate indication, confirm the correct dosing regimen, and provide alternative recommendations if applicable.

The 2 administration benchmarks involve timely administration of the drug within 30 minutes from order placement and timely administration of the AA infusion dose after the loading dose. Although it is ideal for a STAT priority medication be given immediately, this goal may be difficult to achieve. Because AA is not commonly used, this medicine comes from the central pharmacy in our institution. Therefore, we set a target of 30 minutes from the order time to the start of the administration. This 30-minute window has 2 components: (1) time for the pharmacy to prepare and dispense the medicine to the nurse staff (goal $<$ 15 minutes), and (2) time to administer the medicine once available to the nursing staff (goal $<$ 15 minutes). The second administrative benchmark involves the timely administration of the AA infusion dose after completion of the loading dose. Interestingly, none of the dosing sets in our study met all the administrative benchmarks. Although this study was not designed to assess AA's efficacy, administration delays may decrease its efficacy and increase the risk of death from life-threatening bleeding. The original ANNEXA-4 study protocol[11] recommended starting the infusion dose within 2 minutes of completing the loading dose. To allow for some flexibility in case of a delay, our benchmark gave up to 10 minutes between the end of the loading dose and the start of the infusion dose.

Assuming accurate documentation of time stamps, our results show significant delays in dispensing the medication from the pharmacy, starting the initial loading, and starting the infusion dose after completing the loading dose. To reduce dispensing and administration delays, we recommend reviewing the current workflow to identify areas to improve efficiency. Regarding the time between the loading and infusion dose, we hypothesize that nursing staff may not be familiar with how to administer AA correctly. Pharmacy staff and nursing education may help to

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improve dispensing and administration but can be a challenge owing to the high number of nurses in the hospital and owing to regular staff turnover. One recommendation would be to provide targeted education and simulation to critical care and emergency room nurses because they are more likely to administer AA. Another recommendation would be to educate and "certify" the charge nurse on each floor or in specific units like the intensive care unit or emergency department. This practice would ensure that a trained individual is available at all times to give AA.

As alluded to earlier, AA has been reported to increase the risk of thromboembolic events and death. However, it is not always clear in the reported literature how much time has elapsed from AA administration to the thrombotic or fatal event or whether other comorbid conditions also contributed to adverse events. To our knowledge, there is no standard guideline on how soon a thrombotic or fatal event should occur after AA administration to implicate it as a causative etiology. It is, therefore, conceivable that reported thrombotic and death rates may be overestimated, and we recommend that the effect of other comorbid conditions be reported in future literature.

The ANNEXA-4 study[11] reported thrombotic and mortality rates as 10% and 14% at 30 days, respectively. Although direct comparison across studies is not feasible, it initially appears that our study reports higher thrombotic (5 patients, 25%) and mortality rates (7 patients, 35%) within 6 weeks of AA administration (Table 5). On a further review, however, we believe that other factors partially influenced these adverse events. As noted earlier, 2 of the 7 fatalities did not have thrombotic complications and died from intracerebral hemorrhage. The remaining 5 experienced thrombotic complications. Two patients with intracranial hemorrhage and atrial fibrillation developed multifocal cerebral infarcts on day 3 after AA. One received the recommended low dose (patient 1) and one received high-dose AA instead of the indicated low dose (patient 2). Both these patients had a poor Glascow Coma Score on clinical presentation, so their cause of death was listed as intracranial hemorrhage.

While further study is needed, it is reasonable to assume that the greatest potential risk of thrombosis from AA would be within 24 hours after administration. Pharmacokinetic studies report a mean terminal half-life of AA ranging from 3.91 to 6.47 hours in rivaroxaban studies, and 8.06 to 8.21 hours in edoxaban studies.[21] With these numbers, less than 1% of the original AA dose should be present in the plasma by day 3 post AA. Therefore, an alternative plausible explanation for multiple ischemic infarcts on day 3 after AA in patients 1 and 2 is a cardioembolic event from atrial fibrillation not on anticoagulation. Patient 3 also had atrial fibrillation but developed multifocal ischemic infarcts within 24 hours of AA. The short time after AA does implicate AA as the potential etiology and raises the concern for AA administration in patients with last DOAC dose more than 18 hours before. This patient was discharged on day 8 after AA and died after being found unresponsive on day 9. The fact that she was discharged 1 day before suggests that her multifocal cerebral infarcts were unlikely severe enough to contribute to her death. Patient 4 also received low-dose AA more than 18 hours after the last DOAC but did not develop a pulmonary embolism until day 19 after AA. This thrombotic event and later death were believed to be due to progressive metastatic lung cancer and pneumonia rather than from AA. Finally, patient 5 received AA as preoperative DOAC reversal before surgery for an incarcerated ventral hernia. Later the same day, he developed an ischemic bowel and returned to the operating room where he was found with massive pulmonary embolism and mesenteric vein thrombosis. His AA regimen included a high nonstandard loading dose without an associated infusion dose. It is unknown whether he would have had the same adverse outcome if he had received a low-dose loading and infusion.

In conclusion, we believe that there is a more compelling argument for at least 1 thrombotic event (5%) with a standard AA dose but with the caveat mentioned earlier (patient 3). There may be 1 potentially fatal event (5%) linked to AA in our study (patient 5), but he might have received a higher than recommended dose as previously explained. Our data involved a high level of granularity to accurately understand which adverse events could have been prevented in our patient population.

We also recommend that future studies also provide granular data to avoid overestimating the rate of adverse events from AA. Our study is limited by its small sample size and single-center design, so conclusive data regarding the rates of thrombosis and mortality from AA cannot be determined.

CONCLUSION

DOAC-reversal agents such as AA are high-risk medications and may come with a high financial cost. Inappropriate prescription practice may jeopardize patient safety, and all efforts should be made to mitigate these risks. Despite a small sample size, our study highlights some challenges with ordering and administering AA at our institution. It provides practical recommendations that can be implemented at any institution to potentially improve patient safety and prevent adverse events. Further multi-institutional prospective studies, however, are needed to show such a benefit.

POTENTIAL COMPETING INTERESTS

The authors declare no conflicts of interest. Given his role as Editorial Board Member, Dr Aaron Spaulding had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

Abbreviations and Acronyms: **DOAC**, direct oral anticoagulants; **AA**, andexanet alfa

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