Andexanet alfa

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Abstract

Andexanet alfa, an antidote for the anticoagulant medications rivaroxaban and apixaban, is used in cases of uncontrolled bleeding requiring rapid reversal of anticoagulation. This decoy molecule neutralizes the anticoagulant effects of these medications by binding to them in the bloodstream. Andexanet alfa is administered intravenously in emergency situations and should be closely monitored by healthcare professionals. It is essential for patients on direct oral anticoagulant therapy to be aware of this antidote's availability in emergencies or surgeries. This abstract summarizes the usage and considerations of andexanet alfa based on various studies and case reports, emphasizing its role in managing bleeding associated with factor Xa inhibitors. It also highlights potential complications related to its use, such as interactions with heparin, and the need for further research to fully understand its safety and effectiveness.

Introduction

Andexanet alfa, sold under the trade name Andexxa among others, is an antidote for the medications rivaroxaban and apixaban when reversal of anticoagulation is needed due to uncontrolled bleeding. It has not been found to be useful for other factor Xa inhibitors. It is given by injection into a vein.

It works by acting as a decoy molecule that binds to the DOACs in the bloodstream, effectively neutralizing their anticoagulant effects. This allows the patient's blood to clot normally and helps control bleeding.

It's important to note that andexanet alfa is typically used in emergency situations when rapid reversal of anticoagulation is necessary. Healthcare professionals administer it intravenously, and its use should be carefully monitored by medical personnel. Patients on DOAC therapy should be aware of this antidote and its potential availability in case of emergencies or surgical procedures.

Case reports point out that andexanet alfa can cause unresponsiveness to heparin, leading to catastrophic events. As a result, regulatory bodies have issued warning notices to avoid heparinization parallel to the use of andexanet alfa.

Although well-known to hematologists, the phenomenon is underrecognized among stroke clinicians. However, patients with intracranial hemorrhage frequently undergo endovascular or surgical interventions that require periprocedural administration of heparin [1)].

Andexanet alfa (AA), a factor Xa-inhibitor (FXi) reversal agent, is given as a bolus followed by a 2-hour infusion. This long administration time can delay EVD placement in intracerebral hemorrhage (ICH) patients [2)].

Systematic Review and Meta-analysis

A total of 36 studies met the criteria for inclusion, with a total of 1832 patients (967 receiving 4-factor prothrombin complex concentrate [4F-PCC]; 525, andexanet alfa [AA]; 340, idarucizumab). The mean age was 76 (range, 68-83) years, and 57% were men. For 4F-PCC, anticoagulation reversal was 77% (95% CI, 72%-82%; I2 = 55%); all-cause mortality, 26% (95% CI, 20%-32%; I2 = 68%), and thromboembolic events, 8% (95% CI, 5%-12%; I2 = 41%). For AA, anticoagulation reversal was 75% (95% CI, 67%-81%; I2 = 48%); all-cause mortality, 24% (95% CI, 16%-34%; I2 = 73%), and thromboembolic events, 14% (95% CI, 10%-19%; I2 = 16%). Idarucizumab for reversal of dabigatran had an anticoagulation reversal rate of 82% (95% CI, 55%-95%; I2 = 41%), all-cause mortality, 11% (95% CI, 8%-15%, I2 = 0%), and thromboembolic events, 5% (95% CI, 3%-8%; I2 = 0%). A direct retrospective comparison of 4F-PCC and AA showed no differences in anticoagulation reversal, proportional mortality, or thromboembolic events.

Conclusions and Relevance: In the absence of randomized clinical comparison trials, the overall anticoagulation reversal, mortality, and thromboembolic event rates in this systematic review and meta-analysis appeared similar among available DOAC reversal agents for managing ICH. Cost, institutional formulary status, and availability may restrict reversal agent choice, particularly in small community hospitals [3)].

Randomized controlled trials

Connolly et al. randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15

hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P = 0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti-factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P = 0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.) [4)]

Case series

There are no randomized trials comparing andexanet alfa and 4-factor prothrombin complex concentrate (4F-PCC) for the treatment of factor Xa inhibitor (FXa-I)-associated bleeds, and observational studies lack important patient characteristics. Singer et al. pursued this study to demonstrate the feasibility of acquiring relevant patient characteristics from electronic health records. Secondarily, they explored outcomes in patients with life-threatening FXa-I-associated bleeds after adjusting for these variables. They conducted a multicenter, chart review of 100 consecutive adult patients with FXa-I-associated intracerebral hemorrhage (50) or gastrointestinal bleeding (50) treated with andexanet alfa or 4F-PCC. We collected demographic, clinical, laboratory, and imaging data including time from last factor FXa-I dose and bleed onset. R The Mean (SD) age was 75 (12) years; 34% were female. Estimated time from last FXa-I dose to bleed onset was present in most cases (76%), and patients treated with andexanet alfa and 4F-PCC were similar in baseline characteristics. Hemostatic efficacy was excellent/good in 88% and 76% of patients treated with andexanet alfa and 4F-PCC, respectively (P = 0.29). Rates of thrombotic events within 90 days were 14% and 16% in andexanet alfa and 4F-PCC patients, respectively (P = 0.80). Survival to hospital discharge was 92% and 76% in andexanet alfa and 4F-PCC patients, respectively (P = 0.25). The inclusion of an exploratory propensity score and treatment in a logistic regression model resulted in an odds ratio in favor of andexanet alfa of 2.01 (95% confidence interval 0.67-6.06) for excellent/good hemostatic efficacy, although the difference was not statistically significant. Important patient characteristics are often documented supporting the feasibility of a large observational study comparing real-life outcomes in patients with FXa-I-associated bleeds treated with andexanet alfa or 4F-PCC. The small sample size in the current study precluded definitive conclusions regarding the safety and efficacy of andexanet alfa or 4F-PCC in FXa-I-associated bleeds [5)].

A total of 19 patients were enrolled, all of whom had intracranial hemorrhage; 16 patients were evaluable for efficacy. Median percent reduction in anti-FXa activity from baseline to nadir was 95.4% in patients taking apixaban, 96.1% in patients taking rivaroxaban, and 82.2% in patients taking edoxaban. Overall, 14/16 patients (88%) achieved excellent or good hemostasis (apixaban, 5/5; rivaroxaban, 6/7; edoxaban, 3/4). Within 30 days, treatment-related adverse events (AEs) and serious AEs occurred in 2 and 5 patients, respectively. One patient died during follow-up, and 2 patients experienced thrombotic events.

Conclusion: Treatment with andexanet alfa rapidly reduced anti-FXa activity with favorable hemostatic efficacy in Japanese patients with acute major bleeding. Serious AEs of thrombotic events during rapid reversal of anti-FXa activity arose as particular safety concerns in this population as with previous studies [6)].

Lipski et al. evaluated and compared clinical outcomes in patients who experienced intracranial hemorrhage (ICH) while taking apixaban or rivaroxaban and were reversed with four-factor prothrombin complex concentrates (4F-PCC) or andexanet alfa (AA). This retrospective cohort included adult patients who received 4F-PCC or AA for the initial management of an apixaban- or rivaroxaban-associated ICH. A primary outcome of excellent or good hemostatic efficacy at 12 h post-reversal was assessed. Secondary outcomes evaluated were change in hematoma volume size at 12 h, functional status at discharge, need for surgical intervention or additional hemostatic agents post-reversal, new thrombotic event within 28 days, 28-day all-cause mortality, discharge disposition, and hospital and intensive care unit lengths of stay. A total of 70 patients were included (4F-PCC, n = 47; AA, n = 23). For the primary outcome analysis, 21 patients were included in the 4F-PCC group and 12 in the AA group. The rate of effective hemostasis was similar between the 4F-PCC and AA groups (66.7% vs 75%, p = 0.62). There were no statistically significant differences between the groups for secondary outcomes, including 28-day mortality (40.4% vs 39.1%, p = 0.92) and thrombotic complications within 28 days of reversal (17.0% vs 21.7%, p = 0.63). In patients who experienced an ICH while taking apixaban or rivaroxaban, 4F-PCC and AA were found to have similar rates of excellent or good hemostatic efficacy [7)].

Twelve patients with FXi-related ICH were included (EVD placement post-AA bolus, N = 8; EVD placement post-AA infusion, N = 4). Each arm included one patient with bilateral EVD placed. There was no difference in the incidence of new hemorrhages, with one post-AA bolus patient having a small, focal, nonoperative extra-axial hemorrhage. Morbidity and mortality were higher in post-AA infusion patients (mRS, post-AA bolus, 4 [4-6] vs. post-AA infusion 6 [5,6], p = 0.24 and post-AA bolus, 3 (37.5 %) vs. post-AA infusion, 3 (75 %), p = 0.54, respectively). One patient in the post-AA bolus group had a thrombotic event. There was no difference in hospital LOS (post-AA bolus, 19 days [12-26] vs. post-AA infusion, 14 days [9-22], p = 0.55) and ICU LOS (post-AA bolus, 10 days [6-13] vs. post-AA infusion, 11 days [5-21], p = 0.86).

Ammar et al. report no differences in the incidence of tract hemorrhage, extra-axial hemorrhage, or intraventricular hemorrhage post-AA bolus versus post-AA infusion. Larger prospective studies to validate these results are warranted [8)].

A total of five patients, including four outside hospital transfers, received 4F-PCC prior to AA for FXa-inhibitor-associated ICH (n = 3 apixaban, n = 2 rivaroxaban; n = 4 ICH, n = 1 TBI). The doses of 4F-PCC ranged from 25 to 60 units/kg and were administered within a range of 1.5-4.2 h prior to AA. One patient required surgical intervention with craniotomy and three patients underwent external ventricular drain placement. Two of the five patients developed an ischemic or thromboembolic complication within one week from 4F-PCC and AA administration. This case series discusses multiple unique patient cases in which 4F-PCC and AA were both administered for FXa-inhibitor-associated ICH. The results highlight the potentially increased thrombotic risk associated with combination use. Ongoing post-marketing data collection of real patient case scenarios is essential to the establishment of consensus guidelines on how to prioritize initial reversal efforts and manage these patients during the course of their bleed [9)].

Case reports

An 84-year-old woman receiving rivaroxaban for AF presented with impaired consciousness after a head injury. Computed tomography (CT) revealed right ASDH. The patient was administered AA and underwent craniotomy. Although the hematoma was entirely removed, she developed multiple cerebral infarctions 10 h after the surgery. These infarctions were considered cardiogenic cerebral embolisms and rivaroxaban was therefore resumed on the same day. This case indicates the possibility of early cerebral infarction after using a specific reversal agent for factor Xa inhibitors.

Most studies suggest that the safest time for resuming anticoagulants after using reversal agents is between 7 and 12 days. The present case showed that embolic complications may develop much earlier than expected. Early administration of anticoagulant may allow for adequate prevention of acute thrombotic syndromes [10)].

Multiple Choice Test: Andexanet Alfa and Anticoagulant Reversal

What is the primary purpose of Andexanet alfa? a. To prevent blood clots b. To treat hypertension c. To rapidly reverse anticoagulation in cases of uncontrolled bleeding d. To manage diabetes

Which anticoagulant medications can Andexanet alfa reverse? a. Warfarin b. Aspirin c. Rivaroxaban and apixaban d. Heparin

How does Andexanet alfa work to reverse anticoagulation? a. It increases the body's production of clotting factors. b. It binds to anticoagulant medications in the bloodstream, neutralizing their effects. c. It directly dissolves blood clots. d. It reduces platelet aggregation.

In which situations is Andexanet alfa typically used? a. Routine outpatient care b. Chronic anticoagulant therapy c. Emergency situations with uncontrolled bleeding d. Preventive measures for heart disease

What is the recommended route of administration for Andexanet alfa? a. Oral tablets b. Intramuscular injection c. Intravenous injection d. Subcutaneous injection

Why is it important for patients on direct oral anticoagulant therapy to be aware of Andexanet alfa? a. To request it for routine use b. To use it as a daily supplement c. To have it available in emergencies or surgeries d. To use it as a replacement for their regular anticoagulant medication

What potential complication is associated with the use of Andexanet alfa in relation to heparin? a. Enhanced effectiveness of heparin b. No interaction with heparin c. Unresponsiveness to heparin d. Decreased bleeding risk with heparin

In which medical scenarios is Andexanet alfa's effect underrecognized among clinicians? a. Oncology care b. Cardiac surgery c. Stroke management d. Gastrointestinal endoscopy

What is the typical administration method for Andexanet alfa when used as a factor Xa inhibitor reversal agent? a. Bolus injection b. Continuous infusion c. Oral medication d. Sublingual tablet

What is one of the challenges mentioned in using Andexanet alfa for intracerebral hemorrhage patients? a. Rapid reversal b. Difficulty in accessing veins c. Delay in EVD placement due to the long administration time d. Patient non-compliance

Answers:

c. To rapidly reverse anticoagulation in cases of uncontrolled bleeding c. Rivaroxaban and apixaban b. It binds to anticoagulant medications in the bloodstream, neutralizing their effects. c. Emergency situations with uncontrolled bleeding c. Intravenous injection c. To have it available in emergencies or surgeries c. Unresponsiveness to heparin c. Stroke management a. Bolus injection c. Delay in EVD placement due to the long administration time

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