Received: 23 January 2024 | Accepted: 7 April 2024

DOI: 10.1002/ams2.954

ACUTE MEDICINE & SURGERY WILEY

CASE REPORT

Three cases of neutralization of factor Xa inhibitors with andexanet alfa under rotational thromboelastography monitoring

Takeshi Yagi[1] | **Reina Kawano**[1] | **Takuto Tomokage**[1] | **Ryo Ayata**[1] | **Yasutaka Koga**[1] | **Kotaro Kaneda**[1] | **Motoki Fujita**[1] | **Nanami Yamanaka**[2] | **Naomasa Mori**[3] | **Ryosuke Tsuruta**[1]

[1]Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, Ube, Japan

[2]Department of Neurology and Clinical Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, Japan

[3]Department of Neurosurgery, Yamaguchi University School of Medicine, Ube, Japan

Correspondence
Takeshi Yagi, Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, 1-1-1, Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan.
Email: tyagi@yamaguchi-u.ac.jp

Abstract

Background: Factor Xa inhibitors are direct oral anticoagulants that are extremely useful in clinical applications, safe, and do not require dose adjustment. It is desirable to be able to monitor their effects in the event of hemorrhagic complications requiring neutralization. However, it is difficult to monitor their activity and neutralization using conventional coagulation tests.

Case Presentation: We report three patients taking factor Xa inhibitors who underwent rotational thromboelastography (ROTEM) monitoring before and after neutralization with andexanet alfa. All three patients had hemorrhagic complications that required neutralization of their factor Xa inhibitors using andexanet alfa. One ROTEM parameter, the EXTEM clotting time (EXTEM-CT), was immediately shortened after andexanet alfa bolus administration, without subsequent extension of the EXTEM-CT assessed 4 h after the bolus dose.

Conclusion: ROTEM parameters, particularly EXTEM-CT, might be useful for monitoring neutralization of factor Xa inhibitors.

KEYWORDS
andexanet alfa, clotting time, DOAC, factor Xa inhibitor, ROTEM

INTRODUCTION

Factor Xa inhibitors are a type of direct oral anticoagulants (DOACs). They are widely used worldwide because they are as effective as warfarin for preventing embolisms but with less risk of bleeding complications.[1–3] The anticoagulant effect is not routinely monitored in patients using factor Xa inhibitors; however, in patients with hemorrhagic complications, it is desirable to monitor the effects of factor Xa inhibitors, especially if their neutralization is being considered.

Although it is difficult to monitor factor Xa inhibitor using conventional coagulation tests, it has been reported that rotational thromboelastography (ROTEM), a viscoelastic coagulation test, is useful for evaluating the effects of factor Xa inhibitors.[4] Here, we describe three patients with severe bleeding complications in which factor Xa inhibitors were neutralized using andexanet alfa under ROTEM monitoring.

CASE PRESENTATION

Case 1

A 77-year-old man was admitted to our intensive care unit (ICU) because of multiple trauma, including small bilateral hemothorax and multiple rib fractures. Although his general condition was stable after initial resuscitation, a venous thromboembolism was diagnosed on Day 15 of hospitalization. Therefore, apixaban was initiated at a daily dose of

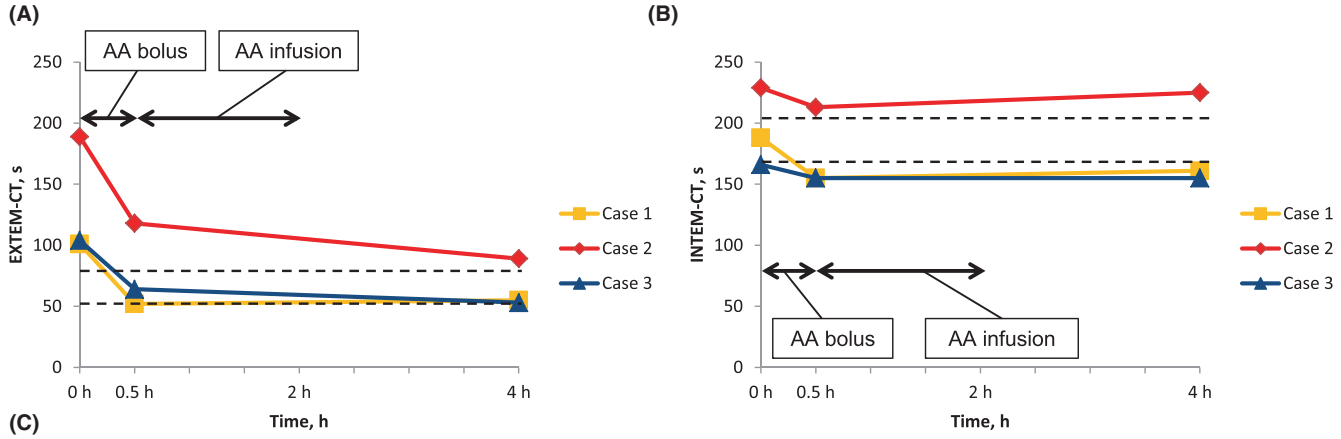
20 mg. On Day 17, he showed signs of shock and based on the imaging tests, he was diagnosed with hemorrhagic shock owing to exacerbation of hemothorax. Therefore, rapid infusion and thoracic drainage were performed. Contrast-enhanced computed tomography showed no evidence of extravasation, and the drainage was considered to be venous hemorrhage. Therefore, we treated him conservatively with anticoagulant neutralization using andexanet alfa, which was administered as a bolus dose of 800 mg in 30 min, followed by infusion of 960 mg over 2 h. The results of the conventional coagulation tests and ROTEM before and after andexanet alfa administration are shown in Figure 1, and the temogram before and after andexanet administration are shown in Figure S1. The extrinsic coagulation pathway clotting time (EXTEM-CT) was immediately shortened after the bolus dose of andexanet alfa and was not prolonged at 4 h after administration. The intrinsic coagulation pathway (INTEM)-CT was slightly shortened after andexanet alfa administration. On Day 21 of hospitalization, he was restarted apixaban at a daily dose of 10 mg without further exacerbation of hemothorax.

Case 2

A 69-year-old man was admitted to our ICU because of neuro-Bechet disease. He had a history of deep venous thrombosis and was receiving apixaban. On Day 15 of hospitalization, he went into septic shock from aspiration pneumonia and required vasopressor. On Day 16 of hospitalization, he suddenly developed respiratory failure, and invasive mechanical ventilation was performed. His blood examination showed acute kidney injury, probably associated with septic shock and prolonged PT and APTT. The cause of coagulopathy could have been an elevated blood concentration of apixaban associated with acute kidney injury or sepsis-associated coagulopathy. Bloody secretions were found in the trachea after endotracheal intubation. Based on his clinical course and imaging findings, he was diagnosed with alveolar hemorrhage due to apixaban. Because of persistent alveolar hemorrhage, andexanet alfa was administered to neutralize apixaban. Andexanet alfa was administered as a bolus dose of 400 mg in 15 min, followed by infusion of 480 mg over 2 h. The results of conventional coagulation tests and ROTEM before and after andexanet alfa administration are shown in Figure 1 and the temogram before and after andexanet administration are shown in Figure S1. EXTEM-CT was clearly shortened after andexanet alfa administration. There were no significant changes in INTEM-CT. His alveolar hemorrhage resolved without exacerbation and on Day 31 of hospitalization, he was restarted apixaban at a daily dose of 10 mg without recurrence of alveolar hemorrhage.

Case 3

A 78-year-old woman was referred to our hospital for the treatment of traumatic brain injury, which included cerebral



	PT-INR			APTT, s		
	Pre AA (0 h)	Post AA bolus (0.5 h)	Post AA div (4 h)	Pre AA (0 h)	Post AA bolus (0.5 h)	Post AA div (4 h)
Case 1	1.59	-	1.33	33.3	-	32.5
Case 2	2.50	1.82	2.26	42.8	45.5	42.8
Case 3	0.96	0.99	0.96	23.8	24.5	25.9

FIGURE 1 Time course of coagulation tests before and after andexanet alfa administration in each case. (A) EXTEM-CT. Dotted lines represent the reference range; (B) INTEM-CT. Dotted lines represent the reference range. (C) PT-INR and APTT. AA, andexanet alfa; APTT, activated partial thromboplastin time; EXTEM-CT, extrinsic coagulation pathway clotting time; h, hour; INTEM-PT, intrinsic coagulation pathway clotting time; PT-INR, prothrombin time international normalized ratio; s, seconds.

contusion and acute epidural hematoma. Head computed tomography on arrival at our hospital revealed the hematoma had increased in size compared with the prior computed tomography. Because she was treated with edoxaban at a daily dose of 30 mg for atrial fibrillation, she was administered andexanet alfa as a bolus dose of 400 mg in 15 min, followed by infusion of 480 mg over 2 h. The results of the conventional coagulation tests and ROTEM before and after andexanet alfa administration are shown in Figure 1 and the temogram before and after andexanet administration are shown in Figure S1. EXTEM-CT was immediately shortened after andexanet alfa administration. There were no significant changes in INTEM-CT. After andexanet alfa administration, craniotomy was performed to remove the hematoma. Bleeding was not a problem during surgery. She did not experience rebleeding or enlargement of the hematoma during her postoperative course. On Day 7 of hospitalization, she was restarted edoxaban at a daily dose of 30 mg without recurrence of intracranial hemorrhage.

DISCUSSION

Factor Xa inhibitors are safer than warfarin. They do not usually require therapeutic monitoring, but their effects cannot be monitored using conventional coagulation tests.[1–5] Nevertheless, the European trauma guidelines recommend measuring the plasma levels of the factor Xa inhibitor or anti-Xa activity in patients taking factor Xa inhibitors, but these are difficult to measure in clinical settings.[5,6] Therefore, an objective parameter that could be used to monitor the effects of factor Xa inhibitors, other than measuring anti-Xa activity, would be extremely useful in clinical settings.

Being able to monitor the effects of Xa inhibitors can also be useful when it is necessary to neutralize these drugs. Neutralization of factor Xa inhibitors should be considered in patients with life-threatening hemorrhagic complications, such as intracranial hemorrhage or trauma.[6,7] Andexanet alfa is currently available for neutralization of factor Xa inhibitors. However, because the conventional coagulation tests do not reflect the activity of Xa inhibitors, the effects of andexanet alfa cannot be monitored in clinical situations. Even in our three patients, the prothrombin time international normalized ratio (PT-INR) before and after andexanet alfa administration also did not show a consistent trend, with a decrease in Case 1, a decrease and then an increase in Case 2, and a flat trend in Case 3 (Figure 1). The results of our cases also suggest that it was difficult to evaluate the effects of Xa inhibitors or andexanet alfa using conventional coagulation tests.

ROTEM is a point-of-care viscoelastic coagulation test used to monitor coagulation in various clinical situations, including cardiac surgery and trauma. In ROTEM, the CT is the time it takes for clotting to begin in whole blood, and EXTEM and INTEM are indicators of the extrinsic and intrinsic coagulation pathways, respectively. Although Seyve et al. reported a linear correlation between the plasma levels of factor Xa inhibitors and EXTEM-CT, a ROTEM parameter, there are few reports on the application of ROTEM in clinical settings.[4] In our cases, EXTEM-CT was immediately shortened after andexanet alfa administration, suggesting that ROTEM can be used to monitor the activity of Xa inhibitors and neutralizing effects of andexanet alfa. Therefore, our report might be a useful demonstration of the possibility of using ROTEM to monitor coagulation function before and after andexanet alfa administration, which has been difficult to assess in clinical settings.

Monitoring factor Xa inhibitors using ROTEM has several limitations. First, the CT determined by ROTEM can be affected by mechanisms other than factor Xa inhibitors, such as the patient's underlying condition or the use of other drugs that affect coagulation activity. Second, some factor Xa inhibitors, particularly apixaban, have been reported to show relatively weak correlations with EXTEM-CT.[4]

CONCLUSIONS

We have described three patients whose factor Xa inhibitors were neutralized by andexanet alfa under ROTEM monitoring. ROTEM parameters, especially EXTEM-CT, might be useful as a point-of-care test for monitoring neutralization of factor Xa inhibitors, which has been difficult to assess with conventional coagulation tests in clinical settings.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed consent: Consent for publication was obtained from the patients or their families.
Registry and the registration no. of the study: N/A.
Animal studies: N/A.

REFERENCES

1. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
3. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
4. Seyve L, Richarme C, Polack B, Marlu R. Impact of four direct oral anticoagulants on rotational thromboelastometry (ROTEM). Int J Lab Hematol. 2018;40:84–93.
5. Jonathan D, Dorothy MA, Shannon MB, et al. 2021 update of the International Council for Standardization in Haematology recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost. 2021;121:1008–20.

6. Rossaint R, Afshari A, Bouillon B, Cerny V, Cimpoesu D, Curry N, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care. 2023;27:80.
7. Demchuk AM, Yue P, Zotova E, Nakamya J, Xu L, Milling TJ Jr, et al. Hemostatic efficacy and anti-FXa (factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. Stroke. 2021;52:2096–105.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yagi T, Kawano R, Tomokage T, Ayata R, Koga Y, Kaneda K, et al. Three cases of neutralization of factor Xa inhibitors with andexanet alfa under rotational thromboelastography monitoring. Acute Med Surg. 2024;11:e954. https://doi.org/10.1002/ams2.954