

Successful Use of Recombinant Activated Factor VII to Reverse Ticagrelor-Induced Bleeding Risk: A Case Report

Anne Godier^{1,2,3} Mélanie Dupont¹ Jean-Philippe Desilles^{4,5,6} Caroline Le Guerinel⁷
Guillaume Taylor¹ Mathilde Perrin¹ Anne-Céline Martin^{2,3,8} Pascale Gaussem^{2,3,9}

¹Service d'Anesthésie-Réanimation, Fondation Adolphe de Rothschild, Paris, France

²Sorbonne Paris Cité, Faculté de Pharmacie, Université Paris Descartes, Paris, France

³INSERM UMR-S1140, Paris, France

⁴Département de Neuroradiologie Interventionnelle, Fondation Adolphe de Rothschild, Paris, France

⁵Sorbonne Paris Cité, Laboratory of Vascular Translational Science, Université Paris Diderot, Paris, France

⁶INSERM UMR 1148, Paris, France

⁷Département de Neurochirurgie, Fondation Adolphe de Rothschild, Paris, France

⁸Service de Cardiologie, Service de Santé des Armées, Hôpital d'Instruction des Armées Percy, Clamart, France

⁹Service d'hématologie Biologique, AP-HP, Hôpital Européen Georges Pompidou, Paris, France

Address for correspondence Anne Godier, MD, PhD, Service d'Anesthésie-Réanimation, Fondation Rothschild, 25-29 Rue Manin, 75019 Paris, France (e-mail: agodier@fo-rothschild.fr).

TH Open 2018;2:e346–e349.

Abstract

Keywords

- antithrombotic
- platelet transfusion
- recombinant activated factor VII
- reversal
- ticagrelor

Management of ticagrelor-associated bleeding is challenging, especially in neurosurgery. Platelet transfusion is inefficient and no antidote is currently available. We report here the first case of recombinant activated factor VII (rFVIIa) use to bypass ticagrelor-induced platelet inhibition. A woman treated with ticagrelor and requiring emergent neurosurgery for an intracranial hematoma received preoperative high-dose platelet transfusion and 60 µg/kg rFVIIa. Laboratory monitoring demonstrated that platelet transfusion failed to reverse ticagrelor-induced platelet inhibition while rFVIIa improved hemostasis by shortening the thromboelastometric clotting time. Neurosurgery occurred without any bleeding event but the patient presented with a postoperative pulmonary embolism. In conclusion, rFVIIa may decrease ticagrelor-induced bleeding risk but careful assessment of the benefit-risk balance is warranted before using rFVIIa to reverse ticagrelor effects.

The major safety issue with antiplatelet agents is bleeding. Ticagrelor is an orally available, direct-acting, selective, and reversibly binding P2Y₁₂ receptor antagonist approved as first-line therapy for the treatment of acute coronary syndrome.¹ Management of ticagrelor-associated bleeding is challenging, especially in neurosurgery: platelet transfusion, usually recommended to reverse antiplatelet agents, is inefficient;

desmopressin is unlikely to be an effective therapeutic agent for control of ticagrelor-associated bleeding risk; and no specific antidote is currently available.^{2,3} The summary of product characteristics for ticagrelor suggests that recombinant activated factor VII (rFVIIa) “may increase hemostasis” (although unlabeled use).¹ Indeed, rFVIIa is a potent hemostatic bypassing agent that boosts thrombin generation by

received
May 9, 2018
accepted after revision
August 20, 2018

DOI <https://doi.org/10.1055/s-0038-1672211>.
ISSN 2512-9465.

© 2018 Georg Thieme Verlag KG
Stuttgart · New York

License terms



massive activation of the extrinsic pathway of the coagulation cascade.⁴ It is approved for the treatment of bleeding disorders including hemophilia with inhibitors but also Glanzmann's thrombasthenia with antibodies to glycoprotein IIb-IIIa or human leukocyte antigen. It has previously been shown to reduce clopidogrel-enhanced blood loss after punch biopsy in healthy subjects.⁵ An *in vitro* study using blood samples spiked with ticagrelor reported that rFVIIa accelerates thrombin generation, and thus clot formation, and therefore may decrease ticagrelor-induced bleeding as observed in a mouse model.^{6,7} However, no clinical data support rFVIIa efficacy to reverse ticagrelor. We report here the first case of rFVIIa used to bypass ticagrelor-induced platelet inhibition with a good clinical outcome. The patient gave informed consent for the publication of this case report.

A 58-year-old woman underwent an elective endovascular stent-assisted coiling of a right unruptured middle cerebral artery aneurysm after a 24-hour premedication with dual antiplatelet therapy combining ticagrelor 90 mg twice daily and aspirin 250 mg per day. Aneurysm perforation occurred during coil deployment, inducing intracranial bleeding with intracerebral hematoma, intracranial hypertension, and mass effect, eventually followed with stent thrombosis. Emergent decompressive craniectomy and hematoma removal were needed. Classified as high bleeding risk surgery as all neurosurgical procedures, this procedure required careful preoperative correction of hemostasis, and international guidelines propose to correct platelet function in patients with aspirin- or P2Y₁₂ receptor antagonists-associated intracranial hemorrhage before neurosurgical procedures.⁸

To reach this aim, platelet transfusion and rFVIIa administration were proposed. High-dose platelet transfusion was performed using two ABO-compatible, irradiated, pooled, random-donor platelet concentrates, stored for 2 days, resulting in 9.9×10^{11} transfused platelets, equivalent to 20 platelet units (PU) (irradiated platelets were oddly provided as such by the blood bank but unrelated to the patient status). The total amount of transfused platelets represents 2- to 2.5-fold the French recommended dose for a 80-kg patient (recommended dose of 0.5 to 0.7×10^{11} platelets/10 kg).⁹ Platelet transfusion was immediately followed by the administration of 60 µg/kg rFVIIa; then, the patient was transferred straightaway to the operating room.¹⁰ Craniectomy and hematoma removal were performed, the surgery lasted 1.5 hours, no bleeding complication occurred, and hemostasis was reported as normal by the neurosurgeon. The postprocedural cerebral computed tomography showed no further hemorrhage but a thoracic computed tomography performed to detect potential rFVIIa-associated thrombotic events revealed a segmental pulmonary embolism, requiring progressive therapeutic anticoagulation with heparin and then with vitamin K antagonists. Three months later, the patient was discharged, conscious but with residual left hemiplegia related to the ischemic stroke downstream stent thrombosis.

—**Fig. 1** summarizes platelet and coagulation monitoring during hemostatic treatment. Monitoring included (1) platelet count, (2) VerifyNow (Accumetrics, San Diego, California,

United States), a standardized point-of-care device that assesses platelet reactivity to antiplatelet agents on whole blood with two different cartridges, one for aspirin and one for P2Y₁₂ receptor antagonists,¹¹ (3) flow cytometric assay for platelet vasodilator-associated stimulated phosphoprotein (VASP) phosphorylation to specifically monitor P2Y₁₂ receptor inhibition (Becton Dickinson, Le Pont-de-Claix, France),¹¹ and (4) rotational thromboelastometry (ROTEM, Werfen, Barcelona, Spain) to assess the extrinsic pathway of coagulation (EXTEM test), especially the clotting time, defined as the time to clot initiation and the clot firmness.¹² Before platelet transfusion, *i.e.*, 14 hours after last antiplatelet therapy intake, platelet inhibition in response to aspirin (VerifyNow-Aspirin) and ticagrelor (VerifyNow-P2Y₁₂ and VASP) was present with respective values below the admitted platelet reactivity thresholds for antithrombotic efficacy.^{11,13} Since the patient received only two doses of ticagrelor before the procedure, ticagrelor-induced platelet inhibition was lower than usually described in case of long-term therapy.¹⁴ The transfusion of 10 PU reversed the effect of aspirin as shown by the leap of VerifyNow-Aspirin result above the threshold value. The total 20 PU (9.9×10^{11} transfused platelets) increased platelet count with a percentage of platelet recovery approaching 100% but failed to reverse ticagrelor-induced platelet inhibition, as both VASP and VerifyNow-P2Y₁₂ values remained below thresholds. rFVIIa had no effect on platelet function but improved hemostasis by shortening the EXTEM clotting time, whereas maximum clot firmness remained unchanged.

This observation confirms that platelet transfusion, as already well documented, readily and promptly corrects aspirin effects. On the contrary, high-dose platelet transfusion is inefficient to reverse ticagrelor, as previously reported in a few case reports^{15–19} and a small case series.³ Indeed, circulating ticagrelor and its active metabolite, present at high plasma concentrations, immediately inhibit the transfused platelets. Moreover, this case suggests that rFVIIa may bypass ticagrelor effects by boosting coagulation: rFVIIa binds to tissue factor, increases thrombin generation, and improves hemostasis, and thus it may overcome platelet inhibition.²⁰ Although this report only suggests a relationship between rFVIIa and bleeding control, rFVIIa currently appears as the only potential option to improve hemostasis in ticagrelor-treated patients facing severe bleeding, especially when emergent neurosurgery is needed. We hypothesized that rFVIIa alone would result in the same hemostasis improvement; therefore, platelet transfusion, although performed here to comply with previous guidelines, may not be necessary. Specific tests performed here to assess respective effects of both platelet transfusion and rFVIIa on hemostasis did not impact therapeutic strategy. Thus, they do not seem to be required before rFVIIa administration in such a context. Last, this observation also underlines that thromboembolism is a common and potentially serious side effect of rFVIIa, which should be closely monitored.²¹

In conclusion, rFVIIa may decrease ticagrelor-induced bleeding risk but careful assessment of the benefit–risk balance is warranted before using rFVIIa to reverse ticagrelor effects.

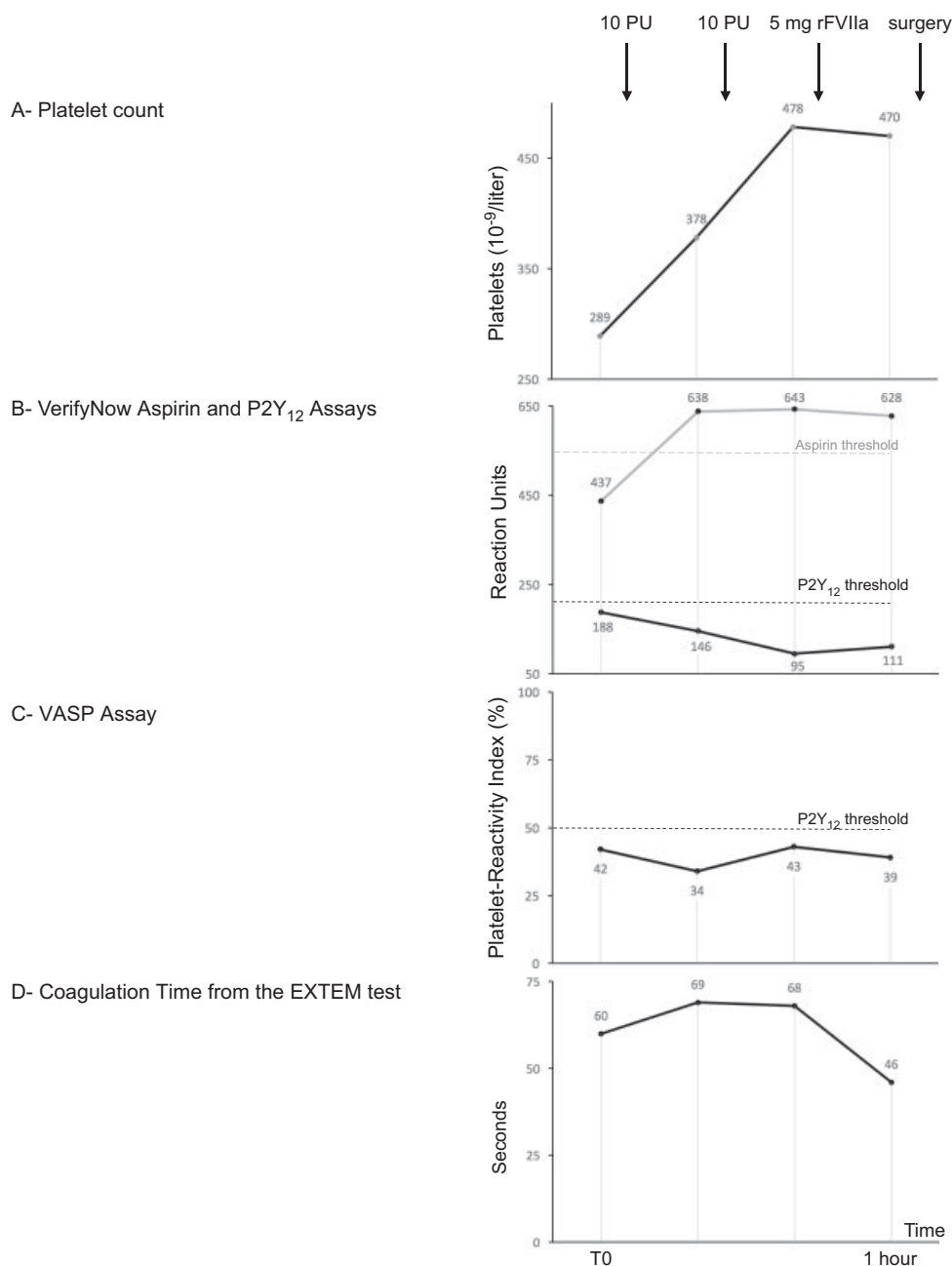


Fig. 1 Platelet and coagulation monitoring during hemostatic treatment. Monitoring included platelet count ($10^9/\text{L}$), VerifyNow-Aspirin (aspirin reaction units), VerifyNow-P2Y₁₂ (P2Y₁₂ reaction units), VASP assay (platelet reactivity index, %), and EXTEM test from the ROTEM device (clotting time, seconds). Dashed lines show platelet reactivity thresholds for antithrombotic efficacy for each test.^{11,13} PU: platelet unit (1 PU is equivalent to 0.5×10^{11} transfused platelets; thus, the total dose of transfused platelets was 9.9×10^{11} platelets); rFVIIa: recombinant activated factor VII; T0: time immediately before platelet transfusion.

Conflict of Interest
None declared.

References

- 1 EMEA. Ticagrelor, product information. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/001241/WC500100494.pdf. Accessed January 2018
- 2 Teng R, Mitchell PD, Butler K. The effect of desmopressin on bleeding time and platelet aggregation in healthy volunteers administered ticagrelor. *J Clin Pharm Ther* 2014;39(02):186–191
- 3 O'Connor SA, Amour J, Mercadier A, et al; ACTION Study Group. Efficacy of ex vivo autologous and in vivo platelet transfusion in the reversal of P2Y₁₂ inhibition by clopidogrel, prasugrel, and ticagrelor: the APTITUDE study. *Circ Cardiovasc Interv* 2015;8(11):e002786
- 4 Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. *J Thromb Haemost* 2012;10(08):1478–1485
- 5 Skolnick BE, Shenouda M, Khutoryansky NM, Pusateri AE, Gabriel D, Carr ME. Reversal of clopidogrel-induced bleeding with rFVIIa in healthy subjects: a randomized, placebo-controlled, double-blind, exploratory study. *Anesth Analg* 2011;113(04):703–710
- 6 Calmette L, Martin AC, Le Bonniec B, et al. Ticagrelor reversal: *in vitro* assessment of four haemostatic agents. *J Clin Pathol* 2017;70(09):733–739

- 7 Pehrsson S, Hansson K, Nelander K, Nylander S. Boosting the coagulation restores haemostasis in ticagrelor-treated mice. *Blood Coagul Fibrinolysis* 2016;27(08):913–919
- 8 Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016;24(01): 6–46
- 9 Recommandation de Bonne Pratique. Transfusion de plaquettes: produits, indications. Available at: https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-11/recommandations_-_transfusion_de_plaquettes.pdf. Accessed July 2018
- 10 Lavigne-Lissalde G, Aya AG, Mercier FJ, et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. *J Thromb Haemost* 2015;13(04): 520–529
- 11 Le Quellec S, Bordet JC, Negrier C, Dargaud Y. Comparison of current platelet functional tests for the assessment of aspirin and clopidogrel response. A review of the literature. *Thromb Haemost* 2016;116(04):638–650
- 12 Lang T, Bauters A, Braun SL, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. *Blood Coagul Fibrinolysis* 2005;16(04):301–310
- 13 Tantry US, Bonello L, Aradi D, et al; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013;62(24):2261–2273
- 14 Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120 (25):2577–2585
- 15 Godier A, Taylor G, Gaussem P. Inefficacy of platelet transfusion to reverse ticagrelor. *N Engl J Med* 2015;372(02):196–197
- 16 Maillard J, Cartier Faessler V, Fontana P, Bonhomme F. Lack of effect of platelet transfusions and desmopressin on intracranial bleeding in a patient receiving ticagrelor. *A A Case Rep* 2015;4 (12):169–171
- 17 Martin AC, Berndt C, Calmette L, et al. The effectiveness of platelet supplementation for the reversal of ticagrelor-induced inhibition of platelet aggregation: an in-vitro study. *Eur J Anaesthesiol* 2016; 33(05):361–367
- 18 Filatre L, Pham DT, d'Ostrevy N, Tran HT, Camilleri L, Azarnoush K. Inefficacy of platelet transfusion in a heart transplant patient under continuous ticagrelor. *J Cardiothorac Vasc Anesth* 2017;31 (05):1776–1778
- 19 Willeman T, Marlu R, Böhle H, et al. Lethal cerebral hemorrhage after ticagrelor intoxication: a specific antidote is urgently needed. *Clin Toxicol (Phila)* 2018 (Epub ahead of print); doi: 10.1080/15563650.2018.1480026
- 20 Mackman N. The role of tissue factor and factor VIIa in hemostasis. *Anesth Analg* 2009;108(05):1447–1452
- 21 Godier A, Greinacher A, Faraoni D, Levy JH, Samama CM. Use of factor concentrates for the management of perioperative bleeding: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018; 16(01):170–174