Acute Thrombocytopenia after Initiating Anticoagulation with Rivaroxaban

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Abstract

A 75-year-old man with paroxysmal atrial fibrillation developed a traumatic intracranial hemorrhage during warfarin treatment. The administration of warfarin was stopped and rivaroxaban therapy, a novel oral anticoagulant (NOAC), was started. Immediately, his platelet count decreased to 3.7×10⁴/μL. The platelet count recovered rapidly after cessation of rivaroxaban administration. Development of thrombocytopenia and its rapid recovery was observed again after another administration, and subsequent cessation, of the drug. A diagnosis of rivaroxaban-induced thrombocytopenia was made. The incidence of thrombocytopenia due to NOACs is rare. Careful attention to thrombocytopenia, which is associated with a higher risk for life-threatening bleeding, is therefore necessary during treatment with NOACs.

Key words: drug-induced thrombocytopenia, rivaroxaban, novel oral anticoagulants

Introduction

Novel oral anticoagulants (NOACs), such as dabigatran, rivaroxaban and apixaban, are administrated for patients with non-valvular atrial fibrillation (NVAF) to prevent stroke. NOAC is superior to warfarin in ease of use and efficacy in randomized controlled trials (1-3). Furthermore, the risk of intracranial bleeding is strongly decreased in patients treated with NOACs compared with warfarin. Therefore, NOACs are superior to warfarin in NVAF patients with a high risk of intracranial bleeding. We herein present a patient who developed severe thrombocytopenia soon after receiving rivaroxaban treatment. Thrombocytopenia during anticoagulation is a high risk for life-threatening bleeding. Careful attention not only to bleeding, but also to thrombocytopenia, after initiating rivaroxaban treatment is therefore necessary.

Case Report

A 75-year-old man with paroxysmal atrial fibrillation developed a traumatic intracranial hemorrhage during warfarin treatment for the prevention of stroke. The patient was taking aspirin for ischemic heart disease; warfarin for paroxysmal atrial fibrillation; and amlodipine, telmisartan, pravastatin, furosemide, trichlormethiazide and famotidine. The day before hospitalization, the patient fell down at home and sustained a head contusion. The following day he felt general malaise and was transferred to our hospital.

On admission, the patient’s level of consciousness was abnormal [Japan coma scale 100; Glasgow coma scale 11 (E1, V4, M6)]; his height was 163 cm and his weight was 40.2 kg. His body temperature was 36.3°C, pulse 85 beats/min and regular, and blood pressure was 181/77 mmHg. A physical examination revealed ecchymoma of the right temporal region of his head. A neurological examination revealed left hemiplegia [left upper limb manual muscle test (MMT), 2/5; left lower limb MMT, 3/5]. There were no other obvious neurological findings. Laboratory studies indicated a white blood cell (WBC) count of 8,500/μL, a red blood cell (RBC) count of 281×10⁴/μL, a hemoglobin (Hb) level of 9.3 g/dL, a hematocrit (Ht) level of 27.3%, a platelet count of 16.8×10⁴/μL, a total protein level of 6.7 g/dL,
Figure 1. Head computed tomography (CT) and head magnetic resonance imaging (MRI) during hospitalization. (A) Head CT on admission revealed an acute subdural hematoma and brain contusion in the right frontal lobe. (B) Head CT on day 36, the day following cranioplasty, showed that the intracranial hemorrhage did not recur. (C) Head diffusion-weighted MRI on day 51 revealed an acute brain infarction. (D) Head CT on day 61 revealed an intraventricular hemorrhage with hydrocephalus. (E) The intraventricular hemorrhage improved by day 120. (F) However, the intraventricular hemorrhage recurred at day 137.

an albumin level of 3.4 g/dL, a blood urea nitrogen level of 33 mg/dL, a serum creatinine level of 1.4 mg/dL, a creatinine clearance level of 25.9 mL/min and a total cholesterol level of 149 mg/dL. The Na level was 141 mmol/L, the K level was 4.4 mmol/L, the Cl level was 107 mmol/L, the aspartate aminotransferase (AST) level was 23 U/L, and the alanine aminotransferase (ALT) level was 17 U/L. The lactate dehydrogenase (LDH) level was 195 IU/L, the creatine phosphokinase level was 70 IU/L, the total bilirubin (T-bil.) level was 0.3 mg/dL, the plasma glucose level was 273 mg/dL, and the glycosylated hemoglobin level was 6.2%. The C-reactive protein (CRP) level was 0.52 mg/dL. The prothrombin time-international normalized ratio (PT-INR) was 1.90 and the activated partial thromboplastin time (APTT) was 25.9 seconds.

On head computed tomography (CT) scan, an extensive acute subdural hematoma was seen from the right frontal to parietal region, and a partial cerebral contusion was seen in the right frontal lobe (Fig. 1A). On a head magnetic resonance imaging (MRI) scan, there were no findings to suggest either malignant disease or vascular disease as the cause of the intracranial hemorrhage.

On the first day of admission, 500 units of coagulation factor IX complex and 10 mg of menatetrenone (vitamin K complex) were immediately administered for rapid correction of the PT-INR. A decrease in the PT-INR from 1.90 to 1.43 was confirmed, and cerebral decompression and hematoma evacuation were performed via craniotomy on the same day. After confirming that there was no recurrence of bleeding on hospital day 3, warfarin administration for atrial fibrillation was restarted. Later, warfarin was discontinued on hospital day 22 due to a scheduled cranioplasty and continuous heparin infusion was started. Cranioplasty was performed on hospital day 35 (Fig. 1B). On day 51, right hemiplegia was noted and a head MRI scan showed acute infarction in the left frontal lobe cortex (Fig. 1C), after which no marked changes in the patient’s neurological symptoms were seen. However, when a follow-up head CT scan was conducted on day 61, an acute intraventricular hemorrhage was seen in the left lateral ventricle together with moderate to severe hydrocephalus (Fig. 1D). At that time the APTT was 41.0 seconds (1.6 times that on admission). Continuous
amlodipine, 5 mg; furosemide, 40 mg; and trichlormethiazide, 1 mg) (Fig. 2). Warfarin administration for the recurrent intraventricular hemorrhage was temporarily discontinued, and it was confirmed that there was no exacerbation in the intraventricular hemorrhage. Warfarin administration (1 mg) was then restarted on day 139. However, due to the multiple complications attributed to warfarin therapy since admission, we switched the patient to rivaroxaban, a NOAC for which administration as a suspension via tube is reported to be valid (1). NOACs are associated with less intracranial bleeding than warfarin (2-5). Warfarin was discontinued on day 143, and rivaroxaban (10 mg) was started, after which the platelet count decreased to 7.3×10^4/μL on day 145 (third day after the start of rivaroxaban). On day 150 (eighth day after the start of rivaroxaban), the platelet count had fallen to 3.7×10^4/μL. Because there were no findings that suggested abnormalities in the coagulation or fibrinolytic system or blood cell disorders (WBC count of 4,700/μL, RBC count of 281×10^4/μL, a reticulocyte level of 9.6%, Hb level of 9.3 g/dL, Ht level of 27.3%, T-bil. level of 0.3 mg/dL, LDH level of 195 IU/L, PT-INR 1.02, APTT 37.5 sec, fibrin/fibrinogen degradation products (FDP) level of 5.9, D-dimer level of 1.2, and a fibrinogen level of 265), the patient’s thrombocytopenia was strongly suspected to be drug-induced. On hospital day 150, the drugs being administered

heparin infusion was discontinued and, following heparin neutralization with the administration of protamine, endoscopic hematoma evacuation was performed on the same day. After confirming that there was no recurrence of bleeding postoperatively, heparin was restarted at a lower dose on day 62. There was no recurrence of bleeding even after restarting heparin, and on day 76, administration of warfarin (2 mg) was restarted via a nasogastric tube. The dose was adjusted to a target PT-INR of 1.6-2.0 in consideration of the bleeding risk. Heparin administration was later ceased, and continuous heparin infusion was restarted on day 96. The gastrostomy was performed on day 109. On a head CT scan done on day 120 (Fig. 1E), the intraventricular hematoma had resolved. Therefore, on day 121, administration of warfarin (1.5 mg) was restarted, and on day 126 the administration of heparin was terminated. After warfarin was restarted, the PT-INR stabilized at around 2.0 with 1.5 mg of warfarin. However, on day 137 there was a recurrence of the intraventricular hemorrhage (Fig. 1F). At that time the PT-INR was 2.10. The blood pressure during this course fluctuated in the range of 120-140/60-80 mmHg with administration of antihypertensive agents (telmisartan, 40 mg; amlodipine, 5 mg; furosemide, 40 mg; and trichlormethiazide, 1 mg) (Fig. 2). Warfarin administration for the recurrent intraventricular hemorrhage was temporarily discontinued, and it was confirmed that there was no exacerbation in the intraventricular hemorrhage. Warfarin administration (1 mg) was then restarted on day 139. However, due to the multiple complications attributed to warfarin therapy since admission, we switched the patient to rivaroxaban, a NOAC for which administration as a suspension via tube is reported to be valid (1). NOACs are associated with less intracranial bleeding than warfarin (2-5). Warfarin was discontinued on day 143, and rivaroxaban (10 mg) was started, after which the platelet count decreased to 7.3×10^4/μL on day 145 (third day after the start of rivaroxaban). On day 150 (eighth day after the start of rivaroxaban), the platelet count had fallen to 3.7×10^4/μL. Because there were no findings that suggested abnormalities in the coagulation or fibrinolytic system or blood cell disorders (WBC count of 4,700/μL, RBC count of 281×10^4/μL, a reticulocyte level of 9.6%, Hb level of 9.3 g/dL, Ht level of 27.3%, T-bil. level of 0.3 mg/dL, LDH level of 195 IU/L, PT-INR 1.02, APTT 37.5 sec, fibrin/fibrinogen degradation products (FDP) level of 5.9, D-dimer level of 1.2, and a fibrinogen level of 265), the patient’s thrombocytopenia was strongly suspected to be drug-induced. On hospital day 150, the drugs being administered

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were furosemide (40 mg), valproic acid (1,200 mg), Fluitran (1 mg), telmisartan (40 mg), amlopidine (5 mg), pravastatin (5 mg), rivaroxaban (10 mg), and lansoprazole (30 mg). These drugs had been administered from before admission or from day 1 in the hospital with the exception of rivaroxaban and lansoprazole. Therefore, the newly added rivaroxaban and lansoprazole (starting on day 128) were discontinued as suspected offending drugs, and the patient was switched to continuous heparin infusion. On hospital day 153 (third day after cessation), the platelet count decreased to 3.7×10^4/μL but rapidly recovered afterward. On day 161 (11th day after cessation), the platelet count was 16.4×10^4/μL. At that time we considered the possibility that rivaroxaban was causing the thrombocytopenia, since thrombocytopenia was not listed as an adverse effect on the rivaroxaban package insert (6). We hypothesized that it was most likely the lansoprazole that had caused the thrombocytopenia (7). Considering the cardiogenic cerebral embolism that occurred during hospitalization, the subsequent difficulty in anticoagulation therapy with warfarin, and that rivaroxaban is an agent that can be administered in a suspension via a tube, rivaroxaban was restarted on day 163. However, the platelet count decreased again to 5.2×10^4/μL on day 168 (sixth day after restart) and so rivaroxaban was considered to be the offending drug and discontinued. Afterward, the platelet count rapidly improved to 17.3×10^4/μL on day 182 (13th day after cessation) (Fig. 2).

The plan for subsequent anticoagulation therapy was to use warfarin with careful dose adjustments, and on hospital day 198, the patient was transferred to a rehabilitation hospital for convalescence. During that course, there was no gastrointestinal bleeding or appearance of purpura or hematoma, and a lymphocyte transformation test performed on day 173 was negative for rivaroxaban.

### Discussion

The mechanism of thrombocytopenia due to rivaroxaban is currently unknown. In the present case, the patient had no cell disorders other than thrombocytopenia. Furthermore, once treatment with rivaroxaban was stopped, the platelet count rapidly recovered and there were no findings that suggested increased platelet consumption. Therefore, the thrombocytopenia seen was likely drug-induced and may be the result of drug-dependent antibody production (8, 9). The frequency of thrombocytopenia caused by NOACs appears low (2–4). However, because thrombocytopenia during anticoagulation may be associated with a higher risk of life-threatening bleeding, clinicians should monitor for the development of thrombocytopenia at the initiation of NOAC treatment.

Although there are no reports of thrombocytopenia due to warfarin use, there are reports of thrombocytopenia with NOAC use, albeit at a low frequency (Table). The package insert in Japan for rivaroxaban as of November 2013, which was administered to the present patient, did not mention thrombocytopenia (6). However, 3 of 1,280 patients (0.2%) enrolled in the J-ROCKET AF study were noted as having thrombocytopenia (4). While its frequency is low, thrombocytopenia is thought to be an adverse effect common to NOACs. The criteria for assessing whether or not thrombocytopenia is caused by pharmaceutical products have not been established in Japan. When the USA criteria for assessing thrombocytopenia (10) were applied to this patient, he met the conditions for Level 1: definitive and was diagnosed with thrombocytopenia due to rivaroxaban. The onset mechanism for drug-induced thrombocytopenia is generally: (1) suppressed production of platelets, (2) platelet phagocytosis or general increased consumption, and (3) increased immunological platelet destruction (9). The mechanism of thrombocytopenia due to rivaroxaban and other NOACs is unknown, but in this patient, there were no cell disorders other than thrombocytopenia. Furthermore, when rivaroxaban was stopped, the platelet count increased and there were no findings that suggested increased platelet consumption. Considering these findings, drug-induced thrombocytopenia in this patient was most likely due to the production of drug-dependent antibodies (8). In this mechanism, the drug, by binding reversibly with platelet membrane proteins, induces structural changes in the membrane proteins resulting in new antigen exposure. Since thrombocytopenia is elicited by the production of antibodies to these new antigens, verification of platelet antibodies is necessary.

We have described a case in which acute thrombocytopenia was diagnosed after the administration of rivaroxaban. Thrombocytopenia during the administration of NOACs may lead to severe hemorrhage considering that it occurs during anticoagulation therapy. When introducing an NOAC, measurement of the creatinine clearance and hemoglobin levels for the early detection of an occult hemorrhage is recommended. Changes in the platelet count must be carefully monitored while NOACs are being used in order to avoid hemorrhagic complications.

The authors state that they have no Conflict of Interest (COI).

### References


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