Clinical Case Report

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Routine coagulation test abnormalities caused by rivaroxaban

A case report

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Abstract

Rationale: Rivaroxaban is a non-vitamin K antagonist oral anticoagulant. Current recommendations state that coagulation monitoring is not required, and neither the dose nor dosing interval requires adjustment in response to changes in coagulation parameters when rivaroxaban is used for approved indications. Guidelines mainly discuss the indications for rivaroxaban and non-vitamin K antagonist oral anticoagulants in general; they offer less guidance regarding how to use these medications in specific clinical situations to bridge the gulf between guidelines and clinical practice.

Patient concerns: An 88-year-old man with a long history of atrial fibrillation presented to the hospital with worsening dyspnea and chest pain. Significantly, he had an estimated glomerular filtration rate of 46.7 mL/min. He was prescribed oral rivaroxaban 20 mg once daily. After 7 days, the patient complained of maroon colored stools.

Diagnosis: Laboratory investigations revealed that the patient's prothrombin time (PT) and activated partial thromboplastin time (aPTT) were elevated. Rivaroxaban induced gastrointestinal bleeding was suspected.

Interventions: Rivaroxaban was discontinued and routine coagulation tests were monitored daily.

Outcomes: Two days following the discontinuation of the drug, the bleeding was controlled and hemoglobin was normal, but the PT and aPTT remained abnormal. On the third day after discontinuing rivaroxaban, the patient experienced sudden syncope and pulselessness and expired.

Lessons: This case indicates that in real-world situations, a small number of patients may develop changes in both PT and aPTT during rivaroxaban therapy. Therefore, coagulation monitoring should be considered in patients with risk factors for bleeding, such as elderly patients with renal insufficiency.

Abbreviations: AF = atrial fibrillation, aPTT = activated partial thromboplastin time, DVT = deep vein thrombosis, eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, PaO_2 = arterial oxygen partial pressure, PE = pulmonary embolism, PT = prothrombin time, sPESI = simplified PE severity index, VTE = venous thromboembolism.

Keywords: atrial fibrillation, coagulation monitoring, pulmonary embolism, rivaroxaban

1. Introduction

Rivaroxaban is approved for the prevention of stroke in nonvalvular atrial fibrillation (AF),[1] prevention and treatment of venous thromboembolism (VTE),[2] and prophylaxis against deep vein thrombosis (DVT) after knee and hip replacement surgery.[3] It has a predictable anticoagulant effect, eliminating the need for routine coagulation monitoring. Rivaroxaban also has a better efficacy/safety ratio, fewer food and drug interactions, and a more rapid onset of action, compared with vitamin K antagonists. In accordance with current European Society of Cardiology guidelines, rivaroxaban—as a Xa factor inhibitor—should be considered as a first-choice anticoagulant, based on positive results from a number of outcome trials.[1,4] Herein, we report an AF patient combined with pulmonary embolism (PE) and DVT used rivaroxaban 20 mg once daily. But after 7 days, he presented abnormal routine coagulation tests and gastrointestinal bleeding. Despite discontinuing the rivaroxaban, the condition was deterioration and finally died.

2. Case

An 88-year-old man with a long history of AF presented to the hospital with worsening dyspnea and chest pain. On admission, he was fully conscious, with a blood pressure of 110/75 mmHg and an irregular heart rate of 124 bpm on auscultation. He had no edema in either lower limb. The remainder of his physical examination was normal. His oxygen saturation was 90% on room air, his electrocardiogram showed AF, and his transthoracic echocardiogram revealed a left atrial diameter of 43 mm and an ejection fraction of 51%. Lower limb venous compression

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Table 1

Physical examination and laboratory results.

Results	On admission	4th day after treatment	7th day after treatment	2th day after discontinuation	Reference range
Heart rate, beats/min	124	90	92	98	–
eGFR, mL/min	46.7	46.1	45.4	44.0	–
D-Dimer, pg/mL	>20	3.55	2.83	–	<0.50
NT-proBNP, pg/mL	6223.00	–	6491.00	6104.00	<450.00
PaO_2, mmHg	53.1	50.5	61.1	62.0	80.0–100.0

eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, PaO2 = partial pressure of oxygen.

ultrasonography showed a DVT involving bilateral superficial femoral veins, the left femoral vein, and the left posterior tibial veins. Laboratory tests revealed normal platelets, hemoglobin, electrolytes, liver function tests, cardiac troponin-T, and routine coagulation tests (prothrombin time [PT] and activated partial thromboplastin time [aPTT]); however, his creatinine, estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimer level, and arterial blood gases were abnormal (Table 1). Furthermore, computed tomography pulmonary angiography confirmed the presence of an embolus in the right main pulmonary artery and its branch (Fig. 1). To select the appropriate treatment strategy, the congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female), HAS-BLED=(hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly, and simplified PE severity index (sPESI) scores were calculated. The scores were 3, 2, and 0, respectively. According to the latest guidelines and the randomized controlled trial study on the use of Non-Vitamin K Antagonist Oral Anticoagulant (NOAC), the patient was prescribed oral rivaroxaban 20 mg once daily.[5,6]

After 4 days of oral rivaroxaban, the patient's assays did not change than before oral rivaroxaban (Table 1, Tables 1 and 2). Seven days after the treatment, the patient's heart rate was lower, dyspnea was relieved, oxygenation was improved, and D-dimer values were lower (Table 1); however, he had maroon stools, and his routine coagulation tests were now abnormal (Table 2).

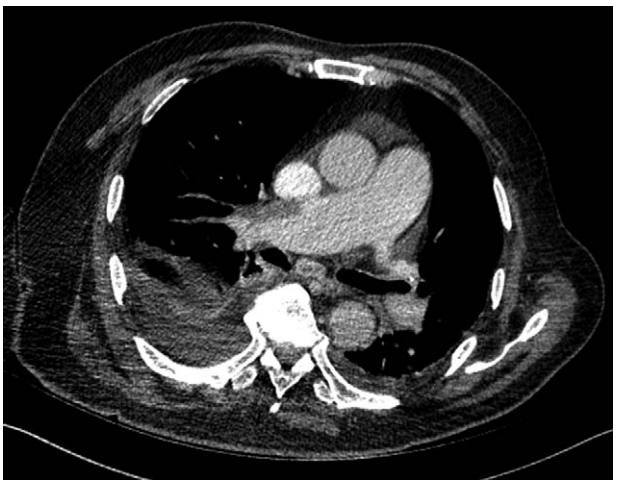

Figure 1. Intraluminal filling defects representing thromboses in the right main pulmonary artery and its branch.

Table 2

Serial coagulation studies.

	PT, second	aPTT, second
Reference range	11.0–15.0	28.0–42.5
On admission	14.8	37.6
4th day after treatment	16.2	40.2
7th day after treatment	>120	174.0
8th day after treatment	>120	178.8
9th day after treatment	>120	176.5

aPTT = activated partial thromboplastin time, PT = prothrombin time.

Rivaroxaban was discontinued and routine coagulation tests were monitored daily (Table 2). Two days after discontinuation, the patient had a small amount of maroon stools, normal hemoglobin, and improved NT-proBNP (Table 1), but his routine coagulation tests remained abnormal (Table 2). On the third day after discontinuing rivaroxaban, he experienced sudden syncope and pulselessness. He was treated according to advanced cardiopulmonary life support protocols. After 30 minutes, spontaneous circulation was unable to be achieved, and further resuscitation attempts were discontinued. Our case report was waived from the First Hospital of Jilin University Ethical Board, based upon their policy to review all intervention and observational study except for a case report. The patient provided informed consent for the publication of his clinical data. The presented data are anonymized and risk of identification is minimal.

3. Discussion

The combination of AF and VTE (PE and DVT) is not only common and complicated to deal with regarding anticoagulation therapy, but it is also associated with substantial morbidity and mortality. Rivaroxaban is used to prevent ischemic stroke in patients with AF and as prophylaxis and treatment of lower limb DVT and PE.[7] Previous studies have shown that excessive rivaroxaban may cause PT prolongation but has no effect on aPTT.[8] Rivaroxaban can produce concentration-dependent prolongation of PT, and the prolonged PT may provide some quantitative information about the risk of bleeding. It should be noted, however, that prolonged PT can be influenced by many other factors as well, including hepatic impairment and vitamin K deficiency.

Before prescribing rivaroxaban, we followed current recommendations that the indications for anticoagulation be based on a careful risk/benefit analysis.[9] The individual patient's profile must be considered, including the patient's age, weight, renal function, liver function, concomitant medications, other comorbidities, and overall frailty. All of these factors may affect the

pharmacokinetics and pharmacodynamics of rivaroxaban.[10,11] Our patient had clear evidence of AF, PE, and DVT. According to several guidelines, anticoagulant therapy was definitely indicated. Considering his age and moderate renal insufficiency, we prescribed only 20 mg orally, but this resulted in gastrointestinal bleeding and significant coagulation abnormalities. We then discontinued the drug, but the patient subsequently developed sudden severe dyspnea and died. Thus, although the patient received 7 days of rivaroxaban and appeared to have a good clinical response, discontinuing the drug resulted in another PE, which was fatal.

Bleeding is a well-known side effect of all anticoagulants, but it is not always associated with elevated concentrations of these drugs. From previous reports of hemorrhage caused by rivaroxaban, only a small number of patients with bleeding treated with a normal dosage had prolonged PT, and none had changes in aPTT. Prolongation of both PT and aPTT was found in only 2 patients consuming large amounts (1960 and 1400 mg orally) of rivaroxaban as a method of suicide.[12,13] Chromogenic anti-factor Xa assays using rivaroxaban calibrators and controls have been shown to accurately measure the anticoagulant effect of rivaroxaban over a wide range of therapeutic levels; however, this assay is not routinely available at most clinical centers.[14] Lack of access to a readily available laboratory test can be a disadvantage when measurement of anticoagulant effect is clinically relevant, such as within the context of a rivaroxaban overdose.

Most studies and guidelines suggest that the use of rivaroxaban does not require coagulation monitoring. Nevertheless, differences between individuals exist in real-world situations, and not only PT but also aPTT prolongation may occur, especially in elderly adults with renal insufficiency. Clinicians should be aware of patients with an increased risk of bleeding and consider monitoring the coagulation status of these individuals during rivaroxaban therapy.

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