Prolonged PT and APTT Results Caused by Combined Usage of Rivaroxaban and Celecoxib: a Case Report

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Case report

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Abstract

Background: Data related to coagulation in patients or changes of coagulation parameters induced by rivaroxaban combined celecoxib remains scarce in a community setting.

Case presentation: We reported a 79-year-old woman was sent to the emergency department of our hospital for intracerebral hemorrhage of left thalamus on February 7th, 2021. On March 25th, after taking rivaroxaban combined celecoxib, her prothrombin time (PT: 23.0 sec) and activated partial thromboplastin time (APTT: 46.3 sec) results were longer than her historical results ((13.0-13.9) sec and (31.7-35.1) sec), the results were not consistent with her clinical symptoms. It turns out that this is unusual side effects of drug combination. After withdrawal the medicine of celecoxib, the results of PT and APTT returned to normal.

Conclusions: Although this situation only occurs in a small number of patients, the accumulation of clinical experience can help doctors save their lives. For boosting the safety of clinical medications, doctors should strengthen the evaluations of bleeding risk.

Background:

Rivaroxaban is widely used in the prevention and treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and reducing the risk of stroke in patients with nonvalvular atrial fibrillation [1]. Celecoxib has been utilized for over 20 years, particularly as an anti-inflammatory, analgesic and antipyretic medication. In recent years, the number of research studies on the antineoplastic effects of celecoxib has increased considerably [2].

Case Presentation:

A 79-year-old women with a history of hypertension and Alzheimer's disease was admitted to the emergency department of our hospital in February 7th, 2021 after a sudden loss of consciousness. Four hours' prior, the patient did not response to voice, nausea and vomiting brown stomach content. On examination, the patient was unconsciousness, not able to speak or blink, left limb was flexion after stimulate. CT scan of head suggested: (a) intracerebral hemorrhage of left thalamus, breaking into ventricular system; (b) cerebral atrophy and chest CT showed: (a) interstitial changes of both lungs with interstitial inflammation; (b) thickening of bilateral pleura; (c) enlargement of heart, calcification of coronary artery and aortic; (d) hiatal hernia. The patient had no history of thromboembolism or clotting disorders, and had no history of smoking or drug abuse.

Two hours later of admission, extraventricular drainage (EVD) was done. The operations were all successfully accomplished. On day 3 of admission, the patient affected with transitory lethargy, poor ability to respond to stimuli, left limb movement after stimulation was observed. The patient could open eyes after stimulation but still not able to speak. After long term lying in bed, pulmonary infection and difficulty in expectoration were observed, tracheotomy was performed for the patient. On day 7, external ventricle drainage tube was removed. On day 8, the patient's mental status progressively improved. Analysis of coagulation tests showed D-dimer (mg/L, DDU)>10.00. There was high risk of embolism. The doctor was concentrating on optimizing the blood vessel examination of extremities. On day 12, B-ultrasound showed right superficial femoral vein (SFV) mural thrombus formation. On day 28, the patient began to take rivaroxaban (Xarelto[®], 10mg, Qd) for anticoagulation. On day 40, the patients' speech ability was improved and tracheostomy tube was removed. The patient could open eyes without stimulation on day 46, and was able to move limbs spontaneously. The patient started taking celecoxib (Baheal pharmaceutical group, 268 Yingcheng Road, Jimo, Qingdao, China) because of backaches. 13 hours later, after taking celecoxib 0.2g. The coagulation tests (STA R Max[®]) of PT and APTT prolonged compare to the historical results (Table 1, Day 47). Given such results, when the laboratory technician found abnormal fluctuation of coagulation results, we started to find the reason step-by-step according to standard operating procedure (SOP).

Firstly, we excluded the possibility reason of specimen. Secondly, we ruled out the cause of the detection system. Everyone knows the importance and effectiveness of quality control programs to ensure standardized laboratory results [3]. Thirdly, there is need to analyze the patient's condition. By analyzing all the tests of the patient during hospitalization, we found the liver function parameters also fluctuated on the same day (Table 2). So what is the reason then? After communicating with the doctor, we found the possible reason was the patient took celecoxib capsules the day before, for a small number of patients, celecoxib and rivaroxaban have associated action in bleeding (unusual side effects). It is also celecoxib, which can cause elevated aspartate aminotransferase (AST) and alanine transaminase (ALT) in some patients (<2%). Therefore, we discussed with the doctor to stop celecoxib and recheck the patient's coagulation parameters. As expected, the patient's coagulation parameters returned to normal (Table 1, Day 48). Based on the improvement of cerebral hemorrhage and the control of pulmonary infection, the patient was discharged on day 50.

Discussion And Conclusions:

This case report, from the perspective of coagulation parameters, provides the first-hand data for early detection of unusual side effects (bleeding risk) after combination usage of rivaroxaban and celecoxib. Although this situation only occurs in a small number of patients, the accumulation of clinical experience can help doctors save their lives, especially for patients with complex conditions. In the past, rivaroxaban was considered as a medical demand for an anticoagulant that can be administered orally and that does not require patient monitoring. In recent years more and more researchers found [4,5], for the few patients, doctors should strengthen the evaluations of bleeding risk after using rivaroxaban combined celecoxib [6,7]. As the performance of each patient varies, doctors are concentrating on understanding the drug interactions better and on optimizing the evaluation methods. It's clearly stated in the fifth chapter of "The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary"[8] that new-oral-anticoagulants (NOAC) and pranason (also belong to nonsteroidal anti-inflammatory drugs (NSAID)) can increase bleeding time by competing with P-glycoprotein. But, it is a great pity that there is still no data on the interaction between rivaroxaban and pranason. This case report provides important detailed first-hand information. This is the first but only one of them. More data needs to be accumulated and summarized in the future. Interaction of NOACs with other drugs usually occurs during the absorption, transport and elimination of these drugs. It is very helpful in providing safe and rapid information about potential interactions when NOACs are used in combination with other drugs, especially during perioperative management [9].

PT was used to monitor rivaroxaban qualitatively. Some scholars found that the prothrombin time may be used to monitor the plasma concentration of rivaroxaban [10]. However, there is variability in the responsiveness of rivaroxaban to different thromboplastins. It's very valuable to share the clinical data. In this case, the patient needs anticoagulation treatment, has bleeding symptoms and has drug synergistic effects. How to balance the mechanism of coagulation and anticoagulation, how to use drugs and how much, we need to accumulate more and more such rare clinical experience. This case report data can also help enhance the prediction of individual rivaroxaban exposure metrics.

List Of Abbreviations:

ALT: alanine transaminase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; DVT: deep vein thrombosis; EVD: extra ventricular drainage; NOAC: new-oral-anticoagulants; NSAID: nonsteroidal anti-inflammatory drugs; PE: pulmonary embolism; PT: prothrombin time; SFV: superficial femoral vein; SOP: standard operating procedure;

Declarations:

Acknowledgments: Not applicable.

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Ethics approval and consent to participate: The experimental protocol was established, according to the ethical guidelines approved by the Human Ethics Committee of the Third Central Hospital of Tianjin. Written informed consent was obtained from patient.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

Conflicts of interest/Competing interests: The authors declare that they have no competing interests.

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Tables:

Table 1 Longitudinal coagulation tests of the patient during hospitalization

Date	PT(sec)	APTT(sec)	Fib(g/L)	TT(sec)	AT α (%)	D-dimer(mg/L,DDU)
Day 1	13.40	34.40	3.46	17.40	71.00	2.89
Day 8	13.90	35.00	3.59	17.50	79.00	>10.00
Day 11	13.00	31.70	3.34	16.50	90.00	6.78
Day 17	13.10	33.70	2.86	18.70	96.00	7.72
Day 25	13.00	35.10	2.75	18.10	95.00	6.31
Day 40	13.00	34.60	4.10	17.10	92.00	1.35
Day 47	23.00	46.30	4.60	17.10	87.00	1.11
Day 48	13.90	37.40	4.13	17.20	81.00	1.04
Normal range	9.7–15.7	32–43	2–4	14–21	80–120	0–0.6

APTT: activated partial thromboplastin time; AT α : antithrombin α activity; Fib: fibrinogen; PT: prothrombin time; TT: Thrombin Time;

Table 2 Longitudinal liver function results from the patient

Date	Alb(g/L) ^a	TBIL(umol/L) ^a	DBIL(umol/L) ^a	INR ^b	AST(U/L) ^a	ALT(U/L) ^a	HGB(g/L) ^c	PLT(10 ⁹ /L) ^c
Day 1	42.7	17.4	2.2	1.01	30	18	127	197
Day 8	30.5	17.6	1.9	1.06	31	28	126	161
Day 11	30.8	13.7	1.7	0.97	53	51	130	180
Day 17	32	14.8	1.9	0.98	50	63	129	171
Day 40	32.9	13.5	1.1	0.97	57	77	134	209
Day 47	34.9	20.7	1.7	2.02	95	124	138	195
Normal range	40–55	3.4–20.5	0–3.4	0.85–1.50	13–35	7–40	115-150	125-350

a, c701/Cobas 8000® analyzer; b, Stago STA-R MAX; c, automated blood cell counter ADVIA 2120i Siemens;

Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBIL: direct bilirubin; HGB: hemoglobin; INR: international normalized ratio; PLT: platelet; TBIL: total bilirubin;