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Original article

Circadian variations in laboratory measurements of coagulation assays after administration of rivaroxaban or warfarin in patients with nonvalvular atrial fibrillation

Yuka Hitaka (MD)[a,b], Masahiro Ogawa (MD, PhD)[a,c,*], Bo Zhang (PhD)[d], Shunichiro Goto (MD)[a], Yoshihisa Nagata (MD, PhD)[a,c], Joji Morii (MD, PhD)[a], Satoshi Imaizumi (MD, PhD, FJCC)[a], Tomoo Yasuda (MD, PhD)[a], Naomichi Matsumoto (MD, PhD)[a,b], Akira Matsunaga (MD, PhD)[b], Keijiro Saku (MD, PhD, FJCC)[a,c]

[a] Department of Cardiology, Fukuoka University School of Medicine, Fukuoka, Japan
[b] Department of Clinical Laboratory, Fukuoka University School of Medicine, Fukuoka, Japan
[c] Endowed Department of Advanced Therapeutics for Cardiovascular Disease, Fukuoka University School of Medicine, Fukuoka, Japan
[d] Department of Biochemistry, Fukuoka University School of Medicine, Fukuoka, Japan

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ABSTRACT

Background: Although rivaroxaban has a relatively shorter half-life and peak and trough plasma concentrations throughout the day than warfarin, rivaroxaban has been found to be non-inferior to warfarin in preventing thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF). We measured circadian variations in laboratory measurements of coagulation assays for chronic treatment with rivaroxaban or warfarin in patients with NVAF.

Methods: We included 28 consecutive patients with NVAF who were treated with rivaroxaban ($n = 13$) or warfarin ($n = 15$). Blood samples were collected at 6 AM, 11 AM, and 3 PM on the same day and on the next morning at 6 AM. Prothrombin time (PT), international normalized ratio of the PT (PT-INR), activated partial thromboplastin time (APTT), prothrombin fragment 1 + 2 (F1 + 2), and protein C level/activity were measured in each patient.

Results: PT and PT-INR were significantly and consistently lower, and the F1 + 2 and protein C level/activity were significantly and consistently higher throughout the day in rivaroxaban-treated patients than in warfarin-treated patients. Significant increases in PT and PT-INR were observed 3 h after oral administration in the patients taking rivaroxaban in the morning, whereas, significant increases in the protein C level/activity were observed 3 h after oral administration in the patients taking warfarin in the morning.

Conclusions: The protein C level/activity was significantly and consistently higher in the rivaroxaban-treated patients than in the warfarin-treated patients throughout the day, which was in contrast to the findings for other coagulation assays. These findings may partly explain the specific persistent anticoagulant effects of rivaroxaban even during the trough phase of the plasma concentration.

Introduction

Warfarin, a vitamin K antagonist, has been the only oral anticoagulant clinically available for many years and is used for anticoagulation in patients with several cardiovascular diseases and conditions, such as atrial fibrillation, venous thrombus, and cardiac valvular diseases, and after surgical valve replacement. Although its effectiveness has been established, warfarin has a narrow therapeutic window and a slow onset and offset of action; it also requires routine coagulation monitoring and dose adjustment because of a considerable variability in the dose response because of many food and drug interactions and some genetic factors. Recently, non-vitamin K antagonist oral anticoagulants

* Corresponding author at: 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Tel.: +81 92 801 1011; fax: +81 92 865 2692.
E-mail address: ogawa0376@gmail.com (M. Ogawa).

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that specifically target factor Xa or thrombin have been developed to overcome the limitations of existing anticoagulants. Rivaroxaban is an orally administered, active, direct factor Xa inhibitor that greatly decreases thrombin generation. The ROCKET AF global clinical trial illustrated that the safety and efficacy of rivaroxaban 20 mg once daily were non-inferior to those of warfarin for preventing strokes and systemic embolisms; this trial also demonstrated the superiority of rivaroxaban in preventing intracranial bleeding in patients with nonvalvular AF (NVAF) [1]. The J-ROCKET AF study demonstrated the safety and efficacy of rivaroxaban 15 mg once daily versus dose-adjusted warfarin in Japanese patients with NVAF and a moderate-to-high thromboembolic stroke risk [2,3]. Although rivaroxaban has a relatively shorter half-life and peak and trough plasma concentrations throughout the day than warfarin [4,5], similar anticoagulant effects for preventing thromboembolic events have been observed for the two drugs in clinical studies. To the best of our knowledge, no previous studies have reported the circadian variations in the anticoagulant effects associated with chronic treatment with these two anticoagulants. The purpose of the present study was to examine and compare the circadian laboratory measurements of coagulation assays after chronic administration of rivaroxaban and warfarin in patients with NVAF.

Materials and methods

Study subjects

From July 2014 to November 2014, plasma blood samples were obtained from 28 consecutive patients with NVAF who had been chronically treated with rivaroxaban ($n = 13$) once daily or with an optimal dose of warfarin ($n = 15$) once daily. These patients had been referred and admitted to the Department of Cardiology, Fukuoka University Hospital for the assessment and treatment of cardiac diseases with AF episodes. The Ethics Committee of Fukuoka University Hospital approved the protocol for the present study, and written informed consent was obtained from all patients.

Blood sample collection and coagulation assays

The patients were instructed to take their medication in the morning between 8:15 and 8:45 AM or in the evening between 6:15 and 6:45 PM. Blood samples were collected at 6 AM, 11 AM, and 3 PM on the same day and 6 AM on the next day (next 6AM). The elapsed times between the morning medication and the blood sample collections were approximately 22 (6 AM), 3 (11 AM), 7 (3 AM), and 22 (next 6 AM) h, respectively. The elapsed times between the evening medication and the blood sample collections were approximately 12 (6 AM), 17 (11 AM), 21 (3 AM), and 12 (next 6 AM) h, respectively. The prothrombin time (PT), international normalized ratio of PT (PT-INR), activated partial thromboplastin time (APTT), prothrombin fragment 1 + 2 (F1 + 2), and protein C level/activity were measured for each blood sample. The coagulation assays used in the present study are shown in Table 1.

Statistical data analyses

The statistical data analyses were performed using SAS (Statistical Analysis System) Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). The statistical differences in the clinical laboratory data and the echocardiography data were analyzed using the Student *t*-test. Categorical variables were analyzed using a chi-squared analysis or Fisher's exact test between the rivaroxaban-treated patients and the warfarin-treated patients. The differences in the continuous variables for the laboratory measurements of coagulation assays between the rivaroxaban-treated patients and warfarin-treated patients were assessed using the Wilcoxon rank-sum test. Changes in the continuous variables at 11 AM and 3 PM on the same day and on the next morning at 6 AM from the baseline (6 AM) were assessed by the Wilcoxon signed-rank test. Data were presented as the mean ± standard deviation, and the significance level (p) was considered to be <0.05, unless indicated otherwise.

Results

Patients characteristics

The clinical characteristics of the enrolled patients are shown in Table 2. Among the 28 consecutive patients with NVAF who were enrolled, 13 received rivaroxaban once daily (6 patients received a dose of 10 mg and 7 received a dose of 15 mg), and 15 were treated with dose-adjusted warfarin (mean dose, 2.7 ± 1.3 mg). In the entire patient population, the mean age was 72 years and 17 patients (61%) were male. The clinical characteristics did not significantly differ between the two drug groups; however, there was a significantly shorter mean follow-up period after anticoagulant administration (10.4 ± 7.7 months vs. 19.6 ± 7.9 months, $p = 0.005$), less use of angiotensin receptor blockers/angiotensin-enzyme converting inhibitors (ARB/ACE-Is) (5/13 vs. 14/15, $p = 0.004$), and a larger left ventricular ejection fraction (59.7% ± 16.1% vs. 46.1% ± 18.6%, $p = 0.048$) in the rivaroxaban-treated patients.

Table 1
An overview of the various assays.

Analyte		Method	Coagulation Analyzer (Manufacturer)
PT	• Thromborel®S	Clotting	COAPRESTA2000®
	(Siemens Healthcare Diagnostics, Murburg, Germany)		(SEKISUI MEDICAL CO., LTD., Tokyo, Japan)
PT-INR	• Thromborel®S	Clotting	COAPRESTA2000®
	(Siemens Healthcare Diagnostics, Murburg, Germany)		(SEKISUI MEDICAL CO., LTD., Tokyo, Japan)
APTT	• Thrombocheck-APTT	Clotting	COAPRESTA2000®
	(SYSMEX CO., LTD., Kobe, Japan)		(SEKISUI MEDICAL CO., LTD., Tokyo, Japan)
F1 + 2	• Enzygnost®	ELISA	–
	(Siemens Healthcare Diagnostics, Murburg, Germany)		
Protein C	• LPIA-ACE PC	Latex photometric immunoassay	LPIA-NV7
	(LSI Medience CO., LTD., Tokyo, Japan)		(LSI Medience CO., LTD., Tokyo, Japan)
Protein C activity	• Test Team®SPLG	Synthetic substrate laws	COAPRESTA2000®
	(SEKISUI MEDICAL CO., LTD., Tokyo, Japan)		(SEKISUI MEDICAL CO., LTD., Tokyo, Japan)

PT, prothrombin time; PT-INR, international normalized ratio of PT; APTT, activated partial thromboplastin time; F1 + 2, prothrombin fragment 1 + 2.

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