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Original article

Clinical usefulness of measuring prothrombin time and soluble fibrin levels in Japanese patients with atrial fibrillation receiving rivaroxaban

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ABSTRACT

Background: Rivaroxaban is currently used to prevent stroke in patients with atrial fibrillation. Measuring coagulation function may help clinicians to understand the effects of this drug and the associated risk of bleeding.

Methods and results: Rivaroxaban was given to 136 patients with non-valvular atrial fibrillation. Mean age was 74.5 ± 9.0 years (men: 63.2%) and mean $CHADS_2$ score (±SD) was 1.8 ± 1.2. Prothrombin times (PTs) and plasma soluble fibrin (SF) levels were examined in 84 out of 136 patients at baseline and at least 2 weeks thereafter. In 48 patients we were able to collect blood at exact times, namely just before and 3 h after rivaroxaban administration, corresponding to the trough and peak concentrations. Mean peak PT in 48 patients was 17.1 ± 3.6 s and median peak SF level was 1.46 μg/mL. Multiple regression analysis showed that female sex, high brain natriuretic peptide, and high dose were independent factors prolonging the peak PT. Patients with peak PTs ≥20 s experienced significantly more bleeding events. Among 29 of 46 patients newly treated with rivaroxaban without any previous anticoagulant, we examined coagulation function at the exact trough and peak times. In 29 patients, peak PT was significantly more prolonged than the baseline or trough PT ($p < 0.001$ for both), whereas trough PT was comparable to the baseline PT. In contrast, both trough and peak SF levels in these newly treated patients were significantly reduced than at baseline ($p = 0.003$ and $p < 0.001$, respectively).

Conclusions: In Japanese patients with non-valvular atrial fibrillation receiving rivaroxaban, a prolonged peak PT (≥20 s) could indicate increased risk of bleeding, and both trough and peak SF levels were reduced relative to baseline. PT and SF are both valuable measures of coagulation status in patients receiving rivaroxaban, regardless of prior anticoagulant history.

Introduction

Anticoagulation therapy is mandatory for preventing stroke in patients with atrial fibrillation (AF) [1–3]. The numbers of patients with AF are increasing, making anticoagulation therapy all the more necessary [4–6]. Over the past 50 years, warfarin has been used in oral anticoagulation therapy, but there are several problems associated with its use. For example, administration of warfarin requires: (1) a fixed period to become effective; (2) adequate patient education for proper compliance; and (3) regular monitoring of the prothrombin time (PT) – international normalized ratio to maintain drug safety and efficacy [7–9].

Recently, novel oral anticoagulants (NOACs) have been proven to be non-inferior to warfarin in terms of preventing ischemic stroke, and they may be superior with respect to the risk of major bleeding [10–13]. Moreover, NOACs do not require frequent monitoring of their anticoagulation effects. However, these findings were obtained in large-scale clinical trials and are applicable only to the types of patients who met the inclusion criteria for each trial. In an actual clinical setting, patients with heart failure or poor medication adherence also need to be treated with anticoagulants. Furthermore, coagulation function must be measured in many other instances,

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such as in patients on anticoagulants undergoing emergency surgery or exhibiting hemorrhage.

Rivaroxaban was the second NOAC to be approved worldwide after dabigatran [10,14]. Data on coagulation function in patients treated with rivaroxaban are limited [15–18], and only Yamashita's group have reported the distribution of PT in Japanese AF patients treated with rivaroxaban [19]. Here, we measured PTs to determine the safety profile of rivaroxaban; we chose PT because it is the most widely used coagulation test. In addition, we measured plasma levels of soluble fibrin (SF), which is generated from thrombin–fibrinogen reactions and is a potentially useful marker of hypercoagulability [20–22].

Materials and methods

Study design and participants

This observational study of Japanese patients with non-valvular AF treated with rivaroxaban was conducted in routine clinical practice at Tosei General Hospital, Aichi, Japan. From 1 May 2012 to 31 May 2013, a total of 136 patients began treatment with rivaroxaban and were considered for study entry. Coagulation function was examined in 84 of these patients at baseline and at least 2 weeks later. In 48 of these 84 patients, we were able to collect blood accurately at times corresponding to the trough and peak concentrations of rivaroxaban. Patients gave written informed consent to participate, and the study was conducted in accordance with the ethical policy of Tosei General Hospital. We also performed outcome and safety evaluations in all 136 patients treated with rivaroxaban. The observation period lasted till 31 December 2013.

Dose of rivaroxaban

Patients received oral rivaroxaban at a dose of either 15 mg once daily (O.D.) or 10 mg O.D. Patients took rivaroxaban after breakfast, and their adherence to medication was monitored. Each dose was determined by the attending physician on the basis of the creatinine clearance (CCr), determined with the Cockcroft–Gault formula, i.e. men, [(140 − age)/(serum creatinine)] × (weight/72); women, 0.85× [(140 − age)/(serum creatinine)] × (weight/72)], or of the presence of a previous history of bleeding complications or concurrent use of antiplatelet drugs, or both. Patients were allocated to three groups: patients who received 15 mg O.D. and had CCr ≥ 50 mL/min; those who received 10 mg O.D. and had CCr < 50 mL/min; and those who received 10 mg O.D. and had CCr ≥ 50 mL/min.

Measuring coagulation function

PTs and SF levels were examined at baseline (before the start of rivaroxaban treatment) and at trough and peak times at least 2 weeks after the start of treatment. We defined the trough time as immediately before the administration of rivaroxaban and the peak time as 3 h after drug administration. Therefore, patients brought the drug with them and then took it orally at the hospital after the first blood collection in the morning. Blood was collected again 3 h later. PT was determined with the recombinant human tissue factor-based thromboplastin reagent (HemosIL Recombi-PlasTin, Instrumentation Laboratory, Lexington, MA, USA). SF was quantified by latex photometric immunoassay (IATRO SF II, LSI Medience Corporation, Tokyo, Japan).

Outcomes

Outcomes were defined in accordance with the ROCKET AF study and J-ROCKET AF study [10,14]. Outcome events included stroke or any other form of embolism in a major organ. In the safety evaluation we counted major and non-major clinically relevant bleeding events. A major bleeding event was defined as clinically overt bleeding associated with a decrease in hemoglobin level of ≥20 g/L, transfusion of ≥2 units of packed red blood cells or whole blood, involvement of an intracranial site, or a fatal outcome. A non-major clinically relevant bleeding event was defined as clinically overt bleeding that did not meet the criteria for major bleeding but that required medical intervention or resulted in the impairment of daily activities.

Statistical analysis

Categorical variables are presented as numbers and percentages (%). Continuous variables are presented as means ± standard deviation or medians. Pearson's correlation was used to measure the strength of the relationship between two variables. To compare PTs between groups we used the unpaired *t*-test, paired *t*-test, chi-square test, or one-way ANOVA. To compare SF levels between groups we used the Wilcoxon signed-rank test or Kruskal–Wallis test. We performed stepwise multiple regression analysis to evaluate the factors affecting peak PT. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted with the SPSS statistical software program (SPSS version 18.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Patient characteristics are shown in Table 1. Mean age of all patients ($n = 136$) was 74.5 years, and 63.2% were men. Eighty-five patients suffered from paroxysmal AF and 51 suffered from persistent or long-standing persistent AF. CCr < 50 mL/min was observed in 30.2% of all patients. During the study, 15.4% of all patients were taking antiplatelet drugs concurrently.

Prothrombin time

The mean trough and peak PTs in the 48-patient group were 11.1 ± 1.0 s and 17.1 ± 3.6 s, respectively (Fig. 1a). Peak PTs were distributed normally and were more significantly prolonged than trough PTs ($p < 0.001$); the trough PTs were comparable to the normal value used in our hospital laboratory (10.9 ± 0.9 s). PTs were compared among the three groups, namely 15 mg O.D. with CCr ≥ 50 mL/min, 10 mg O.D. with CCr < 50 mL/min, and 10 mg O.D. with CCr ≥ 50 mL/min. Baseline PTs were widely distributed within all three groups (12.7 ± 4.2 s, 11.4 ± 1.9 s, and 13.0 ± 2.6 s, respectively) and depended on prior anticoagulant therapy. Trough PTs were comparable among the three groups (11.0 ± 1.0 s, 11.1 ± 0.8 s, and 11.2 ± 1.4 s, respectively; $p = 0.850$) (Fig. 1b) and were not significantly prolonged in each group compared with the normal values used in our hospital laboratory (data not shown). Peak PTs did not differ significantly among the three groups (17.7 ± 3.4 s, 16.7 ± 3.7 s, and 16.9 ± 3.8 s, respectively; $p = 0.725$) (Fig. 1c).

In the 48-patient group, there was no correlation overall between peak PT and CCr ($r = -0.012$, $p = 0.933$; Fig. 2). Moreover, there was no correlation between peak PT and CCr in any of the three groups [15 mg O.D. with CCr ≥ 50 mL/min ($r = -0.01$, $p = 0.972$), 10 mg O.D. with CCr < 50 mL/min ($r = -0.31$, $p = 0.196$), 10 mg O.D. with CCr ≥ 50 mL/min ($r = -0.173$, $p = 0.553$)]. B-type natriuretic peptide (BNP) was negatively correlated with CCr ($r = -0.416$, $p < 0.001$). We also performed a stepwise multiple regression analysis to evaluate the factors affecting peak PT (Table 2). Female sex, high BNP, and high dose were significantly related to peak PT, whereas CCr was not. There were no differences in CCr between male and female patients (males: 63.9 mL/min; females: 63.8 mL/min, $p = 0.987$). Female patients tended to exhibit more prolonged peak