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Regular Article

An analysis on distribution and inter-relationships of biomarkers under rivaroxaban in Japanese patients with non-valvular atrial fibrillation (CVI ARO 1)

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ABSTRACT

Background: Prothrombin time (PT) has been widely used for measuring anticoagulation intensity under rivaroxaban therapy, but precise information has not been well established yet.
Methods: Consecutive 96 non-valvular atrial fibrillation (NVAF) under rivaroxaban between Jan/June 2015 were recruited. Serum concentration (SC) and PT with 5 representative reagents available in Japan (Neoplastin Plus®, Thromborel S®, Thrombocheck PT®, Thrombocheck PT Plus®, and Recombiplastin®) at 2–4 h after (peak) and before intake of rivaroxaban (trough) were measured at outpatient clinic in the cardiovascular institute (CVI ARO study 1). Nonlinear mixed-effects modeling was used to model the population pharmacokinetics and pharmacodynamics of rivaroxaban.
Results: An oral one-compartment model was employed to describe the population pharmacokinetics of rivaroxaban. The pharmacokinetics of rivaroxaban were affected by creatinine clearance, alanine aminotransferase, and use of CYP3A4 or P-gp inhibitors. PTs with 5 reagents were predicted by pharmacodynamic models with SC, hematocrit, serum albumin, and age, with medium predicting ability (highest/lowest R2 = 0.746/0.658 in Recombiplastin/Thromborel S, respectively).
Conclusions: This population analysis in NVAF patients under rivaroxaban therapy demonstrated that pharmacokinetics of rivaroxaban was described by an oral one-compartment model with expected covariates, and can be assessed by PT with available reagents in Japan with medium predicting ability.

1. Introduction

For several decades, warfarin has been the only oral anticoagulant available for prevention of ischemic stroke in patients with atrial fibrillation (AF). Warfarin reduces ischemic stroke risk in patients with AF by approximately two thirds [1], and has been widely used in Japan [2–4] and around the world [5,6]. However, there are several limitations in the usage of warfarin, including a narrow therapeutic window and interactions with many foods and other drugs, requiring continuous monitoring and dose adjustment.

Rivaroxaban, one of the direct oral anticoagulants (DOACs), directly inhibits Factor Xa activity [7]. Due to its predictable pharmacokinetic and pharmacodynamics profiles, monitoring is not primarily recommended. However, in some situations, including severe bleeding or emergent surgery, measurement of anticoagulant markers may be required to judge an excessive anticoagulant effect of rivaroxaban [8,9]. Although anti-Xa activity assay is known to be sensitive for rivaroxaban [9], it is not yet available in daily clinical practice in Japan.

On the other hand, prothrombin time (PT) is a relevant anticoagulant marker that is relatively sensitive for rivaroxaban, although the sensitivity of PT for anticoagulants differs between reagents [9]. As PT reagents are distributed differently between countries, data using prevalent reagents in our own country are required [10], but are still scarce in Japan.

In the present study, we examined the pharmacokinetics of rivaroxaban and the different responses of PT to serum concentration of rivaroxaban with 5 representative reagents in Japan [10] in Japanese patients with non-valvular AF (NVAF) using population pharmacokinetics and pharmacodynamics (PPK/PD) analysis.

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2. Materials and methods

2.1. Objectives

This study is a single-center, contemporary observational study, registering Japanese patients with NVAF who are currently taking rivaroxaban or who are to receive rivaroxaban in daily clinical practice, and accumulating the outcomes during a-half-year follow-up period (UMIN Clinical Trials Registry: UMIN000016424). The primary objective of this study is to obtain the information regarding the clinical efficacy and limitation of PT value in patients with NVAF under rivaroxaban.

2.2. Study population

Consecutive 101 patients with NVAF who were taking rivaroxaban for primary prevention of ischemic stroke in the Cardiovascular Institute between May 1, 2014 and Oct 31, 2014 were registered. Patients with any of the following during the enrolment period were excluded: (1) receiving dual anti-platelet therapy, (2) inadequate dosage of rivaroxaban at PT measurement, (3) rivaroxaban hypersensitivity, (4) river dysfunction with clotting disorder, (5) moderate and high river dysfunction (Child-Pugh classification B or C), (6) renal dysfunction (creatinine clearance <30 mL/min), (7) women who are pregnant or may be pregnant, (8) patients taking HIV protease inhibitor (ritonavir, atazanavir, indinavir, etc), (9) patients taking azole antimycotic agent (itraconazole, voriconazole, ketoconazole, etc., excluding fluconazole), (10) patients taking drugs containing cobicistat, (11) patients taking drugs with strong cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp) derivant (rifampicin, phenytoin, carbamazepine, phenobarbital, Saint John's wort-containing food, etc.), (12) patients with acute bacterial endocarditis, (13) patients who did not give written informed, consents for this study, (14) patients who are judged by the researchers as inadequate for this study.

Finally, 5 patients were excluded because the blood sampling could not be completed. Consequently, 192 samples out of 96 patients were analyzed.

2.3. Ethics and informed consent

This study was performed in conformity to the ethical norms based on the Declaration of Helsinki (revised in 2008) and Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare in Japan, issued in 2014). Informed consent was obtained from all participants in writing. The study protocol of this study was reviewed by the Institutional Review Board in the Cardiovascular Institute.

2.4. Plasma concentration and PD measurement

After obtaining informed consent, plasma samples were collected before (defined as trough) and 2–4 h after drug intake (defined as peak) to measure serum concentrations of rivaroxaban and PT with 5 reagents under rivaroxaban treatment at each time point.

Plasma rivaroxaban concentrations were measured using a validated, selected chromatographic assay with liquid chromatography–tandem mass spectrometry (LC-MS/MS) [11]. Isotope-labeled rivaroxaban was used as an internal standard. The calibration range of the procedure was from 1 ng/mL (lower limit of quantification; LLOQ) to 1000 ng/mL. Quality control samples at concentrations of 2, 50, and 800 ng/mL were determined with an accuracy of 95.9%–106.4%, 100.3%–105.5%, and 96.9%–100.6%, respectively. All samples were stored at −80 °C and analyzed within 12 months after sampling. It was confirmed that the analyte was stable for this time period under frozen storing.

Measurement of PT was performed by mixing of PPP at 37 °C with calcium thromboplastin and determined as an amount of time needed for a sample to form a clot using the photometric method. The different thromboplastin reagents used were Neoplastin Plus® (Roche Diagnostics, Mannheim, Germany); Thromborel S®, Thrombocheck PT®, and Thrombocheck PT Plus® (Siemens Healthcare Diagnostics, Marburg, Germany); and RecombiPlasTin 2G® (Instrumentation Laboratory, Bedford, MA, USA). These reagents were selected because they are currently the most commonly used reagents in Japan [10]. Neoplastin Plus, Thrombocheck PT, and Thrombocheck PT Plus are derived from rabbit brain. RecombiPlasTin 2G contains recombinant human tissue factor, whereas Thromborel S is derived from human placenta. Clotting time of Neoplastin Plus was measured using a STA-compact® coagulometer (Diagnostica Stago, Asnières, France); Thromborel S, Thrombocheck PT, and Thrombocheck PT Plus were measured using a CS-2000i® coagulometer (Siemens Healthcare Diagnostics, Marburg, Germany); and RecombiPlasTin 2G was measured using a ACL-TOP coagulometer (Instrumentation Laboratory, Bedford, MA, USA). All samples were stored at −80 °C and analyzed within 12 months after sampling. The coefficient of variation on within-run reproducibility for the five reagents were less than 1.5% when the PT values were within the average levels, and less than 2% when out of the average levels.

2.5. Population PK-PD evaluation methods

A sequential PK/PD modeling approach was used to analyze the plasma drug concentration and PT measurement profile. First, the population PK models were developed and second, the estimated individual PK parameters were employed to estimate the PD model. All analyses were performed using Phoenix® NLME™ 1.4 software (Certara LP, Princeton, NJ, USA). The first-order conditional estimation (FOCE-ELS) was used for all analyses. Phoenix provides a mixed-effects modeling technique to quantify both unexplained inter-individual variability (IIV) and intra-individual (residual) variability (RUV), as well as the influence of measured concomitant effects or covariates on base model parameters. The inter-individual variabilities were modeled with exponential error model with a normally distributed random variable with a mean of 0 and a variance of ω^2. The intra-individual variability was modeled with exponential or additive error with a mean 0 and a variance of σ^2 for PK and PD measurements, respectively.

Covariates were incorporated into the models if the likelihood ratio test (LRT) showed a reduction in objective function value (OFV) of >3.84 (in the case of one degree of freedom [df]). A decrease by >3.84 points between competing models corresponds to prespecified nominal p values of <0.05.

Covariates to be investigated for any relationship with the estimates of individual rivaroxaban PK-PD parameters (obtained from the base model) were prespecified based on previous knowledge of the PK-PD characteristics of the compound. Age at enrolment (AGE) and body weight (WGHT), sex were tested as covariates on PK or PK-PD parameters. The following covariates were measured at both peak (2–4 h after rivaroxaban intake) and trough (before rivaroxaban intake): serum creatinine (SCRE), creatinine clearance (CCR), albumin (ALBU), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), hematocrit (HCT), and hemoglobin (HB). Although patients with coadministration of strong CYP3A4 or P-glycoprotein derivant (rifampicin, phenytoin, carbamazepine, phenobarbital, Saint John's

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