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Full paper

A study on indices of apixaban anticoagulation: A single-center prospective study

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ABSTRACT

Background: Depending on the characteristics of patients, the blood concentration of apixaban can unexpectedly increase, possibly leading to bleeding events. Anti-FXa activity reflects the apixaban blood concentration; however, measurement of this activity is both time-consuming and expensive. The current study aimed to evaluate the usefulness of routinely measured coagulation indices as future indicators of the efficacy and safety of apixaban.

Methods: Eighteen nonvalvular atrial fibrillation patients administered apixaban (average, 52.5 days) were prospectively enrolled in our hospital. The prothrombin time (PT) and the activated partial thromboplastin time (APTT) were measured by using the Coagpia® Reagent kits.

Results: The PT and the APTT increased significantly after the administration of apixaban (PT: $p < 0.001$, APTT: $p < 0.001$). While the apixaban plasma concentration by evaluating anti-FXa activity was not significantly correlated with the APTT after administration of apixaban, the concentration closely correlated with the PT ($\beta = 0.765$, $p < 0.001$) and the percentage change in the PT from before and after the administration of apixaban ($\beta = 0.650$, $p = 0.005$).

Conclusion: The usefulness of routinely monitoring PT in patients administered apixaban during the ordinary clinical medicine should be investigated further by large clinical trials.

Introduction

Reducing the incidence of an embolism and avoiding adverse bleeding events are both crucial to the use of anticoagulants. The vitamin K antagonist, warfarin, has long been used to prevent strokes in patients with valvular atrial fibrillation or nonvalvular atrial fibrillation. New non-vitamin K antagonist oral anticoagulants (NOACs; dabigatran, rivaroxaban, and apixaban) have been recently developed that, unlike warfarin, do not require coagulation monitoring. In the ARISTOTLE trial involving patients with nonvalvular atrial fibrillation, apixaban, a factor Xa (FXa) inhibitor, was superior to warfarin in terms of inhibiting an embolism and limiting the risk of massive bleeding.[1] Thus, NOACs have overcome the drawbacks of warfarin and yield superior results to warfarin in terms of efficacy. In the 2016 ESC Guidelines for the management of atrial fibrillation, if an oral anticoagulant (OAC) is indicated in a patient eligible to receive an NOAC, then administration of an NOAC is a Class I recommendation with an A level of evidence.[2]

The administration dose of apixaban in adults is 5 mg orally b.i.d. Following administration, patients have an increased risk of bleeding and the blood concentration of the drug may increase if a patient meets two or more of the following criteria: aged ≥80 years, a weights ≤60 kg, or a serum creatinine level ≥1.5 mg/dL. Thus, rules for dose reduction, i.e., a dose of 2.5 mg b.i.d., have been devised.[3] However, there are borderline patients who may or may not fulfill the rules for dose reduction. In addition, the blood

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concentration of a drug can unexpectedly increase depending on the characteristics of the patient administered that drug, such as patients who are elderly, have renal dysfunction, or sarcopenia, leading to bleeding events. A previous study reported that the trough concentration of dabigatran is correlated with the incidence of massive bleeding.[4] The activity of the coagulofibrinolytic system exhibits daily rhythmicity.[5] Thus, the anticoagulant action of a drug should be rapidly and routinely measured in patients in particular situations, such as during emergency surgery, during bleeding, with an increased blood concentration of the drug, or with co-morbidity, in order to reduce adverse reactions and increase the drug's efficacy.[4,6–8] The anticoagulant activity of apixaban is closely correlated with its anti-FXa activity[9]; however, measurement of anti-FXa activity is not routine and is time-consuming and expensive. Accordingly, simple clinical indices to monitor the effects of apixaban need to be established.

The apixaban blood concentration was previously reported to correlate with the prothrombin time (PT) when specific PT reagents are used[10]; however, the correlation varies depending on the reagent.[11] Currently, the PT[9,11] and the PT-INR[12–14] cannot be used as indices to assess the pharmacodynamic characteristics of apixaban, and standard indices to determine the efficacy and safety of apixaban in clinical practice have yet to be established.

Baseline coagulation is known to vary depending on patient characteristics.[15,16] In clinical practice, patients with nonvalvular atrial fibrillation who require an OAC are often elderly, and hence have a high risk of bleeding complications. According to post-marketing surveillance of apixaban, 81% of adverse bleeding reactions occur within 4 weeks of administration.[3] Therefore, examining the correlation between changes in coagulation indices, such as the PT and the activated partial thromboplastin time (APTT), before and after apixaban administration and the apixaban blood concentration is crucial.

Objective

The aim of the current study was to evaluate usefulness of routinely measured PT and APTT as future indicators of the efficacy and safety of apixaban by investigating whether the PT and the APTT after apixaban administration and the percentage change in the PT and APTT from before and after administration of apixaban were correlated with the apixaban plasma concentration calculated based on anti-FXa activity.

Materials and methods

Subject selection

In the current study, potential subjects were patients with nonvalvular paroxysmal or chronic atrial fibrillation who were administered apixaban for the first time. Exclusion criteria were: i) patients who had been switched over to apixaban from another anticoagulant, ii) patients with active cancer, iii) patients with an abnormal PT according to blood collected before administration, iv) patients from whom written consent could not be obtained, and v) patients who would not be available for follow-up as determined by their primary physician or a lead investigator. Eighteen patients consented to participate in this study.

This study was explained in detail to potential subjects, and potential subjects were informed that participation was voluntary. Written consent was obtained from all subjects. Investigators followed the World Medical Association Declaration of Helsinki (amended in October 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects from the Ministry of Health, Labour, and Welfare (amended on December 22, 2014). The protocol for this study was approved by the ethics committee of the Kyoto Medical Center.

Study design

This study was a single-center prospective study. Based on the package insert, apixaban was administered orally to subjects at a dose of 5 mg or 2.5 mg b.i.d.[3] Various items were assessed before and at least 21 days after the start of administration.

Assessment items

The primary outcome measures were the PT, the APTT, D-dimer levels, and the level of anti-FXa activity. Age, sex, height, weight, blood pressure, heart rate, past medical history (hypertension, diabetes mellitus, heart failure, stroke, or vascular disease), concomitant medication (an antihypertensive, dyslipidemia medication, diabetes medication, or other medication), and blood tests (white blood cell (WBC) count, platelet count, serum creatinine (Cr), aspartate aminotransferase (AST), alanine transaminase (ALT), hemoglobin (Hb), and γ-glutamyl transpeptidase (γ-GTP)) were assessed as secondary outcome measures. CHADS-2 score and CHADS2-VASc score were calculated for all subjects.

Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in a sitting position after resting for >5 min using an automatic electronic sphygmomanometer (BP-103iII; Nippon Colin, Komaki, Japan).[17] The regular-sized cuff that is appropriate for Japanese (the arm length: 17–32 cm) was used as recommended.

Measurement of the PT and APTT

The PT and the APTT were measured by the Laboratory of the Kyoto Medical Center using the Coagpia® Reagent kits (Sekisui Medical Co. Ltd, Tokyo, Japan)[18] and a coapresta 2000 (Sekisui Medical Co. Ltd, Tokyo, Japan).[19] Fibrin deposition was measured based on the optical determination of increased turbidity.

Measurement of apixaban plasma concentrations

The apixaban concentration in plasma was measured by the OBM Research Center (Osaka Prefecture, Japan) using the FXa inhibitor Screening Kit (Bio Vision, K362) and an enzyme-linked immunosorbent assay plate reader (Molecular Devices, Spectra Max M3). In this study, apixaban was diluted 2-fold in seven steps to generate a standard curve (0.02–6.25 μM). The concentration of apixaban in plasma samples was calculated based on the standard curve and the level of anti-FXa activity. When results were below the detection limit, analysis was performed with the lower limit of detection (0.02 μM) serving as a substitute value.

Statistical analysis

All statistical analyses were performed by a professional statistician using the Statistical Package for Social Sciences (SPSS) Statistics 17.0 (SPSS Inc., Chicago, IL, USA). The normality was assessed using the Shapiro–Wilk test. Clinical data before and after apixaban administration were compared using the paired t-tests for parametric data or the Wilcoxon signed rank test for non-parametric data. In addition, correlations between the apixaban plasma concentration and coagulation indices were examined using the Pearson's correlation coefficient. The statistical significance level was set at $p < 0.05$.

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