Predicting the Anticoagulant Activity of Apixaban from Prothrombin Time of Warfarin when Replacing Warfarin with Apixaban

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Abstract

Background: Warfarin has a narrow therapeutic window, interacts with some foods, and requires routine monitoring. Direct oral anticoagulants (DOACs) are able to resolve some of the drawbacks of warfarin. Recently, it has been reported that the incidence of major bleeding in patients with atrial fibrillation who are receiving apixaban is similar to that in patients receiving warfarin. We therefore sought indices for measuring/monitoring the anticoagulant activity of apixaban.

Methods: Twenty-three patients (70.0±8.6 years; 17 males, 6 females) with non-valvular atrial fibrillation, for whom warfarin was replaced with 10mg/day apixaban, were enrolled in the study from February 1, 2013 to July 31, 2014. We examined the relationship between prothrombin time of warfarin (PTw) and PT of apixaban (PTa) by using paired t-test. We also used multiple regression analysis to predict PTa from PTw and other factors (age, body surface area, serum creatinine, and creatinine clearance).

Results: PTw was significantly shorter than PTa (PTw, 19.0±3.2s versus PTa, 15.5±1.5s; P < 0.0001), and PTa was significantly prolonged compared with the normal PT range of 10s to 12s (P = 0.01). This finding suggested that PT is sensitive in the prediction of apixaban-associated Xa activity, and PTa could be predicted using PTw as follows: predicted PTa = 10.515 + 0.263×PTw (P = 0.056).

Conclusions: When warfarin was replaced with 10mg/day apixaban, PTa could be predicted using PTw without any routine monitoring to evaluate anticoagulant activity.

ABBREVIATIONS

DOAC: Direct Oral Anticoagulant; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; PT-INR: Prothrombin Time-International Normalized Ratio

INTRODUCTION

Warfarin was used as the only oral anticoagulant for many years; however, direct oral anticoagulants (DOACs) were approved in Europe and the United States a few years ago, and in Japan in March 2013. There is widespread use of DOACs such as dabigatran, rivaroxaban, edoxaban, and apixaban as the new (or novel) oral anticoagulants for the prevention of stroke in patients with non-valvular atrial fibrillation. The reasons for the rapid increase in the use of DOACs are that 1) they do not require frequent monitoring of anticoagulant activity or dose adjustment, 2) their anticoagulant activity is equal to or greater than that of warfarin, and 3) the incidence of side effects (particularly cerebral bleeding) is less than that associated with warfarin [1]. The findings from multicenter retrospective cohort study were that the incidences of hematoma enlargement and mortality in 87 patients presenting with DOAC-associated cerebral hemorrhage were lower than the incidences in those with warfarin-associated cerebral hemorrhage (17% versus 26% and 16% versus 35%, respectively) [1]. However, the results of a recent multicenter observational study showed that the incidences of hematoma enlargement and mortality in 61 patients presenting with DOAC-associated cerebral hemorrhage were 38% and 28% respectively [2]. The results indicate that there were no major differences between the incidences of such major side effects with DOACs and
warfarin. Although routine monitoring of anticoagulant activity or dose adjustment are not required with DOACs, the findings in a recent study indicate that a certain measure of the anticoagulant activity of DOACs is needed to predict the outcomes of stroke.

In order to seek an effective measure of the anticoagulant activity of DOACs, the mechanism of their anticoagulation must be considered. Dabigatran is a direct thrombin (IIa) inhibitor; therefore, activated partial thromboplastin time (APTT) is considered a sensitive test to monitor plasma dabigatran concentrations. Since rivaroxaban, edoxaban, and apixaban are direct Xa factor inhibitors, it is expected that prothrombin time (PT) will be sensitive for monitoring their concentrations in plasma. Actually, APTT is reported to be a sensitive test for assaying dabigatran [3], while PT is used to assay rivaroxaban [4] in plasma. Although PT has been reported as not sensitive to apixaban [5], PT can be measured using two specific reagents, Shinplastin Excel S® (Kyowa Medex Co, Tokyo, Japan) and Coapigia PT-N® (Sekisui Medical Co, Tokyo, Japan), to predict the anticoagulant activity of apixaban [6]. Shinplastin Excel S® and Coapigia PT-N® are tissue thromboplastin reagents from human brain and rabbit brain, respectively. Thrombo-check PT Plus® (Sysmex Co, Kobe, Japan) is used at Nippon Medical School Hospital, and it is the same tissue thromboplastin reagent (rabbit brain) as Coapigia PT-N®.

In this study, we investigated the following points regarding apixaban and PT:

1) Whether PT measured by Thrombo-check PT Plus® was prolonged significantly by apixaban.
2) Whether PT in patients taking apixaban could be predicted by factors such as age, body surface area, serum creatinine, creatinine clearance, or PT, in case of replacing warfarin with apixaban.
3) Whether any event of stroke occurred in patients taking apixaban, after replacing warfarin with apixaban.

**METHODS**

**Subjects**

The study was conducted at Nippon Medical School Hospital. From February 1, 2013 to July 31, 2014, warfarin was replaced with apixaban (5-mg tablet twice daily) in 49 patients. The patients did not satisfy the exclusion criteria for the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). The criteria were: atrial fibrillation of a reversible origin, moderate to severe mitral stenosis, requirement of anticoagulant therapy for an artificial cardiac valve, stroke occurring within 7 days, concurrent administration of aspirin > 165 mg/day or aspirin + clopidogrel, severe kidney dysfunction (serum creatinine > 2.5 mg/dL or estimated creatinine clearance < 25 mL/min) [7]. In 30 of the 49 patients, PT (PTw) was measured within 30 days before replacing warfarin with apixaban and PT (PTa) was again measured 7 days after the replacement. Since the duration of action of warfarin is about 72 hours, warfarin did not affect the measurement of PTa. Seven of the 30 patients took medicines that interact with apixaban, (clopidogrel, 3 patients; aspirin, 2 patients; diltiazem, 1 patient; and celecoxib [non-steroidal anti-inflammatory drug], 1 patient) and were excluded from the study. Finally, 23 patients were recruited for the present study. Since the study was retrospective, the name and identification number of each subject was replaced with a reference number, which met the ethics criteria of the hospital.

**Evaluation**

The medical record of patients were reviewed retrospectively for sex (male/female), age (years), height (cm), body weight (kg), dose of warfarin (mg/day), dose of apixaban (mg/day), serum creatinine (mg/dL), prothrombin time-international normalized ratio (PT-INR) when taking warfarin, PT-INR when taking apixaban, PT when taking warfarin (s), PT when taking apixaban (s), and CHADS, score (points). CHADS, score was calculated as follows: congestive heart failure (1 point), hypertension (1 point), age > 75 years (1 point), diabete mellitus (1 point), and stroke/transient ischemic attack (2 points) [8]. Body surface area was calculated using Dubois’s equation [9]. Estimated creatinine clearance was calculated using the Cockcroft-Gault equation [10]. PT was measured using Thrombo-check PT Plus®.

**Statistical analysis**

Statistical significance was indicated when PTa was significantly prolonged compared with the normal range of 10-12s. PTw was compared with PTa using paired t-test. Assuming that PTa was a dependent variable and the other variables were independent, it was examined whether PTa could be predicted significantly using the independent variables. A priori sample size was calculated in a condition that the anticipated effect size = 0.35, the desired statistical power level = 0.8, the number of predictors = 1, and the probability level = 0.05, and was obtained as exactly 23 [11]. Thus, we investigated whether PTa could be significantly by a single independent variable. Stat View ver.5.0 (SAS Institute Incorporation, North Carolina) was used for the statistical analyses. Statistical significance was considered at P ≤ 0.05 in all cases. Data have been expressed as mean± standard deviation.

**RESULTS**

The clinical characteristics of the patients are listed in Table 1. Apixaban was administered at 10 mg/day; however, the recommended dose is 5 mg/day in non-valvular atrial fibrillation. For sex (male/female), age > 80 years, body weight < 60kg, or serum creatinine > 1.5mg/dL. Three patients who were > 80 years old did not satisfy the criterion of 5 mg/day. One patient had serum creatinine > 1.5mg/dL but did not satisfy the criteria because he was 52 years old and weighed 146.5kg.

PTw (19.0±3.2 s) was significantly higher than PTa (15.5±1.5 s) (paired t-test; P < 0.0001, Figure 1). It was evaluated at the lower level of P ≤ 0.05 whether PTa was significantly prolonged comparing with the normal range, 10 to 12s (P = 0.01). PTa of every subject was prolonged over the normal range (the minimum of PTa = 13.5 s).

Table 2 shows the correlation coefficients between PTa and the other variables. The correlation coefficient between PTa and PTw was the strongest, and was of statistical significance (P = 0.0056). Although the value for the correlation coefficient between PTa and age was the second highest, it was not statistically significant.
Table 1: Clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.0±8.6</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>17/6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.3±8.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63.9±20.8</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.67±0.23</td>
</tr>
<tr>
<td>Dose of warfarin (mg/day)</td>
<td>2.9±0.8</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.86±0.25</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>71.5±19.7</td>
</tr>
<tr>
<td>PT while taking warfarin (s)</td>
<td>19.0±3.2</td>
</tr>
<tr>
<td>PT while taking apixaban (s)</td>
<td>15.5±1.5</td>
</tr>
<tr>
<td>CHADS2 score (points)</td>
<td>2.2±1.3</td>
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*Data reported as mean±standard deviation.

**Abbreviations:** PT: Prothrombin Time

(P = 0.243). Thus, we examined whether PTa could be predicted using PTw, by means of regression analysis as follows:

Predicted PTa = 10.515 + 0.263×PTw (P = 0.056).

The correlation coefficient between predicted PTa and PTa was found to be 0.559.

Two patients suffered from cerebral infarction after replacing warfarin with apixaban. Figure 2 shows the correlation between PTa and predicted PTa; the closer a point is to the diagonal, the better the prediction. The two black-shaded circles in Figure 2 indicate the results for two patients who had the same CHADS2 score of 4 points, and with the same details: 1 point each for hypertension and age, and two points for stroke/transient ischemic attack.

**DISCUSSION**

It was reported that the incidence of major bleeding with apixaban was lower than that with warfarin (2.13% versus 3.09%) among the 18,201 patients in the ARISTOTLE trial [12].

Table 2: Correlation coefficients (r) between prothrombin time and other variables while taking apixaban.

<table>
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<td>PTa</td>
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<td>Age</td>
<td>0.032</td>
<td>0.8844</td>
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<tr>
<td>Body surface area</td>
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<td>0.5499</td>
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<tr>
<td>Serum creatinine</td>
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<td>0.3564</td>
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<td>Creatinine clearance</td>
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Therefore, it might be necessary to monitor the anticoagulant activity of apixaban as well as that for warfarin, in order to prevent major bleeding. This is especially useful in case of an emergency surgery or traumatic hemorrhage. One of the aims in developing DOACs was to avoid frequent monitoring of anticoagulant activity or dose adjustment. We therefore examined whether the anticoagulant activity of apixaban could be estimated from PTw and/or any other parameters in patients when replacing warfarin with apixaban.

Initially, the reasons that PT was unavailable were 1) a small peak-trough variability and 2) poor sensitivity in predicting anticoagulant activity [4]. However, it was reported that PT was prolonged only with Trinitrol PT Excel S® [13]. Thereafter, it was also reported that PT was prolonged with Coagilia PT-N® [6]. The Japanese trade name of Trinitrol PT Excel S® is Shinplastin Excel S®. Because Thrombo-check PT Plus® is the same tissue thromboplastin reagent as Coagilia PT-N®, it was presumed that apixaban-associated Xa activity could be estimated in the same way as was done by Kanemoto et al. [6]. Since PTa was significantly shorter than PTw, it was considered that the sensitivity of PT to the anticoagulant activity of apixaban was lower than that of warfarin. However, in the present study the significant prolongation of PTa over the normal range was presumed to reflect the anticoagulant activity of apixaban. Thus, it was concluded that it was important to select a sensitive reagent.

When warfarin was replaced with 10 mg/day apixaban, PTa could be predicted using PTw measured within 30 days before the replacement. Since P value was almost 0.05 and the correlation coefficient (r = 0.559) was high, PT was considered to be an available index of apixaban-associated Xa activity.

Since monitoring the anticoagulant activity of apixaban is not general requirement, PTa is rarely measured. One of our findings showed that PT while taking apixaban could be predicted from PT measured within 30 days before replacing warfarin with apixaban.

Stroke occurred in two patients after replacing warfarin with apixaban. This suggested that the 10 mg/day dose of apixaban was not adequate to prevent the event in those patients. The patients had a history of stroke/transient ischemic attack and their CHADS2 score was 4 points. These results indicate that it might be necessary to monitor anticoagulant activity in patients who have a history of stroke. The three circles with dots in Figure 3 represent patients who had CHADS2 score ≥ 4 points. One of those patients was 78 years old, had a history of stroke, and had CHADS2 score of 5 points. Because the CHADS2 score was more than the scores of the other two patients who had suffered a stroke, it was predicted that if the level of anticoagulant activity of apixaban is not adequate, patients may have a stroke in the future. The insights obtained from the review of subsequent medical records of the 78-year-old patient showed that the apixaban was replaced with warfarin because of reaction to apixaban.

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Limitations of the present study include the small sample size. The calculated priori sample size was exactly the number of subjects enrolled in the study. Since PTa could not be predicted by more than 2 variables, this study became a simple study with a small number of patients. In future studies, we aim for a probability level ≤ 0.05 by recruiting a larger number of subjects. Even though the sample size was small in the present study, two patients suffered from stroke. Therefore, we will also examine whether the dose of apixaban is sufficient to prevent stroke, by observing more subjects for a longer period in the future study.

CONCLUSIONS

Since PTa was significantly shorter than PTw, the sensitivity of PT to the anticoagulant activity of apixaban was considered lower than that of warfarin. However, in the present study, the significant prolongation of PT over the normal range was presumed to reflect the anticoagulant activity of apixaban. Thus, it was concluded that it was important to select a sensitive reagent to monitor anticoagulant activity. When warfarin was replaced with 10 mg/day apixaban, PTa could be predicted using PTw without routine monitoring to evaluate anticoagulant activity.

REFERENCES
