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Analysis of factors for poor activated partial thromboplastin time control after dabigatran administration

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In this study, we compared patients whose activated partial thromboplastin time (APTT) was prolonged excessively with those whose APTT was controlled within the normal range after dabigatran administration. We analyzed the factors for the APTT prolongation. We divided the patients into two groups: those whose APTTs prolonged to more than 65 s and those whose APTTs were less than 65 s after dabigatran administration. There were 130 patients from March 2011 to July 2013, and we analyzed the background features and laboratory data of these patients. Results showed that there were no significant differences in the patients' background and laboratory data except for the high-density lipoprotein cholesterol (HDL-C) level. However, details of the relationship between the APTT prolongation and the HDL-C level are currently unknown. We hypothesize that the reason for the APTT prolongation is the variability in such parameters as the time of blood drawing, internal time of dabigatran, individual variability, and blood concentration. Therefore, we consider that these parameters need to be carefully evaluated even if APTT does not show prolongation.

1. Introduction

The frequency of atrial fibrillation increases with age, and it develops more frequently in men than in women. An epidemiological survey in Japan showed that the incidences of atrial fibrillation are 3.4% and 1.1% in men and women in their 70 s, and 4.4% and 2.2% in those in their 80 s, respectively (Inoue et al. 2009). The biggest problem associated with atrial fibrillation is that it is a major cause of thromboembolism, regardless of whether the atrial fibrillation is paroxysmal or persistent. Once cerebral embolism occurs, quality of life (QOL) and life prognosis are significantly impaired. The risk of thromboembolism is high for elderly patients. Owing to the increase in the number of patients with atrial fibrillation, the number of those who will develop cardiogenic cerebral embolism may increase further in the future, and there is a possibility that this will also lead to social problems.

We expect that the Japanese population will further age in the future. It is predicted that the number of patients with atrial fibrillation will be more than one million people in 2030; presently, there are approximately 800,000 atrial fibrillation patients (Inoue et al. 2009). The number of patients with atrial fibrillation increases with age, as revealed by the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study (Kannel et al. 1983) in the U.S. Therefore, it is very important to prevent cardiogenic cerebral embolismin Japan; to this end, we consider that it is very important to promote medical health care.

The applicability of a dosage method for dabigatran was evaluated, and the use of this drug has spread rapidly because the measurement of the prothrombin time international normalized ratio (PT-INR), which is required in conventional anticoagulant therapy, is not necessary for this drug. Moreover, dabigatran undergoes fewer interactions than warfarin. However, a warning about bleeding complications was issued in Japan and care should be taken when administering dabigatran. Therefore, studies related to establishing an indication of coagulation after dabigatran administration from the viewpoint of safety were carried out (Stangies et al. 2007; van Raju et al. 2010; Meyer et al. 2012; Douxfils et al. 2012) Activated partial thromboplastin time (APTT) is widely used as an indication of coagulation ability after dabigatran administration. The usefulness of APTT is considered when administering dabigatran because there is a report showing that APTT prolongation and blood dabigatran levels correlate well (Stangies et al. 2007). However, there are few reports that provide sufficient details. It has been reported that hemorrhagic complications were significantly severe in cases when APTT was prolongedto more than 80 s (Connolly et al. 2009).

However, there are few detailed reports on the cause-and-effect relationship concerning excessive APTT prolongation. Therefore, in this study, we compared patients whose APTT was prolonged excessively with those whose APTT was controlled within the normal range after dabigatran administration. We analyzed the factors for the APTT prolongation.

2. Investigations and results

2.1. Patients' background

Table 1 shows patients' background features in the prolonged group (male: 7, female: 3) and in the control group (male: 82, female: 38). There were no significant differences in the following parameters between the two groups: sex, age, weight, body mass index (BMI), primary disease [e.g., heart failure, hypertension, dyslipidemia, diabetes mellitus, stroke, transient ischemic attack (TIA)], $CHADS_2$ scores, initial doses, bleeding after dabigatran administration, combination of dabigatran with drugs (e.g., antiplatelet drugs, p-glycoprotein inhibitors, proton pump inhibitors), history of gastrointestinal bleeding, switching from warfarin to dabigatran, and switching from antiplatelet agents to dabigatran.

2.2. Comparison of laboratory data

Table 2 shows the laboratory data obtained immediately after dabigatran administration for the two groups. There were no significant differences in the following parameters between the two groups: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (γ-GT), blood urea nitrogen (BUN), serum creatinine (Scr), The estimated glomerular filtration rate(eGFR), creatinine clearance (CCr), dose/eGFR, dose/CCr, total cholesterol(T-Cho), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), c-reactive protein (CRP), total protein (TP), serum albumin (Alb),red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), glycohemoglobin (HbA_{1c}), brain natriuretic peptide (BNP), systolic blood pressure (SBPs), and diastolic blood pressure (DBPs). However, the HDL-C levels were 55.2 ± 5.2 mg/dL in the control group and 40.7 ± 10.7 mg/dL in the prolonged-APTT group, which is significantly lower.

3. Discussion

We investigated the factors for APTT prolongation after dabigatran administration. From this study, we revealed that the factor for APTT prolongation is HDL-C. There is a report that low HDL-C level is a risk factor for atrial fibrillation (Watanabe et al. 2008). However, the details of the relationship between the APTT prolongation and the HDL-C levels are currently unknown. We hypothesize that the reason for the APTT prolongation is the variability in such parameters as time of blood drawing, internal time of dabigatran, individual variability, and blood concentration. Therefore, we consider that these parameters need to be carefully evaluated even if APTT is not prolonged. The factor for the poor control of APTT was not determined in this study. We considered the following reasons. First, as the most important point, we considered the effects of both the time of blood drawing and the internal time of dabigatran. When patients take dabigatran in a clinical dose, the blood dabigatran levels reach approximately 150–170 ng/mL and APTT prolongs up to approximately 1.5–1.8 times the normal APTT (Stangier et al. 2007). We considered that APTT varies according to the time of blood drawing after dabigatran administration because dabigatran reaches its maximum level in the blood within 2 h (Wong et al. 2011). However, we were not able to specify in detail the time of blood drawing after dabigatran administration or the internal time because this was a retrospective observational study. We considered that the cause of the variation is that the data that surpassed the peak values were mixed in this study because we used APTT measured 3–6 h after dabigatran administration. Suzuki et al. (2011), divided the outpatients into a customary dose group and the reduced dose group. APTT was measured in the morning or afternoon. Suzuki et al. (2011) compared the distribution of the APTTs between both groups and found that APTT was distributed equally between both morning and afternoon. Therefore, the influence of time of blood drawing on APTT was not recognized between the customary

Table 1: Comparison of patients' background between prolonged-APTT group and control group

Variables	All patients (n = 130)	Prolonaed-APTT group (n = 10)	Control group (n = 120)	*p value*
Male/Female (%)	89 (68.5)/41 (31.5)	7 (70.0)/3 (30.0)	82 (68.3)/38(31.7)	1.0000
Age	68.9 ± 10.7	69.5 ± 8.3	68.9 ± 10.9	0.9686
Weight (kg)	65.1 ± 12.3	61.4 ± 10.2	65.4 ± 12.5	0.3595
BMI (kg/m^2)	24.2 ± 3.4	24.6 ± 5.1	24.2 ± 3.3	0.8049
Heart failure (%)	37(28.5)	4 (40.0)	33 (27.5)	0.4691
Hypertension (%)	85 (65.4)	6 (60.0)	79 (65.8)	0.7371
Dyslipidemia (%)	56(43.1)	4 (40.0)	52 (43.3)	1.0000
Diabetes (%)	29 (22.3)	2 (20.0)	27 (22.5)	1.0000
Stroke (%)	26 (20.0)	3 (30.0)	23 (19.2)	0.4176
TIA (%)	8 (6.2)	0 (0.0)	8 (6.7)	1.0000
$CHADS_2$ scores (point)	1.9 ± 1.4	2.0 ± 1.8	1.9 ± 1.3	0.9037
Initial doses (150 mg) (%)	2 (1.5)	0 (0.0)	2(1.7)	1.0000
(220 mg) (%)	100 (76.9)	7 (70.0)	93 (77.5)	0.6961
(300 mg) (%)	28 (21.5)	3 (30.0)	25 (20.8)	0.4481
Bleeding after dabigatran administration (%)	18 (14.2)	3 (30.0)	15 (12.8)	0.1512
Combination of dabigatran with antiplatelet drugs (%)	13 (10.0)	1 (10.0)	12(10.0)	1.0000
P-glycoprotein inhibitors (%)	43 (33.3)	5 (50.0)	38(31.9)	0.2996
Proton pump inhibitors (%)	74 (56.9)	7 (70.0)	67 (55.8)	0.5136
History of gastrointestinal bleeding (%)	12 (9.2)	0 (0.0)	12(10.0)	0.5973
Switching from warfarin to dabigatran (%)	87 (66.9)	5 (50.0)	82 (68.3)	0.2973
Switching from antiplatelet agents to dabigatran (%)	8 (6.2)	0 (0.0)	8 (6.7)	1.0000

$p < 0.05$ (Student's *t*-test, Mann-Whitney U-test, χ^2 test, Fisher's exact test) Mean $\pm$ S.D.

Table 2: Comparison of laboratory data between prolonged-APTT group and control group

Variables	All patients (n = 130)	Prolonged-APTT group (n = 10)	Control group (n = 120)	*p value*
AST (IU/L)	32.4 ± 23.9	39.7 ± 28.9	31.8 ± 23.5	0.5998
ALT (IU/L)	27.1 ± 23.4	28.1 ± 17.6	27.0 ± 23.9	0.7145
γ-GT (IU/L)	56.9 ± 73.5	120.8 ± 162.0	51.2 ± 58.1	0.0848
BUN (mg/dL)	16.0 ± 5.6	16.6 ± 5.5	16.0 ± 5.6	0.7841
Scr (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.7310
eGFR (mL/min)	64.7 ± 13.2	61.0 ± 14.3	65.0 ± 13.1	0.3885
CCr (mL/min)	58.9 ± 17.1	56.1 ± 17.6	59.1 ± 17.1	0.5439
Dose/eGFR (mg/mL/min)	3.8 ± 1.0	4.3 ± 1.5	3.8 ± 0.9	0.3593
Dose/CCr (mg/mL/min)	4.3 ± 1.4	4.9 ± 2.0	4.3 ± 1.3	0.4315
T-Cho (mg/dL)	195.7 ± 36.9	206.6 ± 23.3	195.1 ± 37.5	0.4994
HDL-C (mg/dL)	54.1 ± 15.3	40.7 ± 10.7	55.2 ± 15.2	0.0055
LDL-C (mg/dL)	110.9 ± 28.1	114.8 ± 26.0	110.6 ± 28.4	0.6902
TG (mg/dL)	146.4 ± 105.6	123.4 ± 56.3	148.2 ± 108.5	0.7603
CRP (mg/dL)	0.3 ± 0.7	0.6 ± 0.6	0.3 ± 0.7	0.0798
TP (g/dL)	7.2 ± 0.5	7.3 ± 0.5	7.2 ± 0.5	0.2901
Alb (g/dL)	4.2 ± 0.4	4.2 ± 0.7	4.2 ± 0.4	0.9472
RBC ($\times 10^6/\mu$L)	4.4 ± 0.6	4.4 ± 0.5	4.4 ± 0.6	0.9655
Hb (g/dL)	14.2 ± 3.3	14.2 ± 1.7	14.2 ± 3.4	0.5759
Hct (%)	41.7 ± 5.0	42.0 ± 5.7	41.7 ± 4.9	0.8740
HbAlc (%)	6.1 ± 1.3	6.0 ± 0.6	6.1 ± 1.3	1.0000
BNP (pg/mL)	132.8 ± 141.4	228.6 ± 185.1	125.2 ± 135.6	0.0606
SBP (mmHg)	128.8 ± 16.9	134.5 ± 22.3	128.3 ± 16.4	0.3759
DBP (mmHg)	77.1 ± 12.6	84.7 ± 16.6	76.5 ± 12.0	0.1183

$p < 0.05$ (Student's *t*-test, Mann-Whitney U-test) Mean ± S.D.

dose group and a reduced dose group. However, in this paper, the time of blood drawing is not specified. In addition, given the pharmacokinetics of dabigatran, as determined by Stangier et al., (2007) it is unlikely that APTT is equal between morning and afternoon. Furthermore, Suzuki et al. (2011) reported that many individuals who showed long APTTs were included in the group of patients who are taking dabigatran at a low dose. They suggested the renal dysfunction and the low bioavailability of dabigatran as the causes. The gastrointestinal absorption rate of dabigatranis approximately 6.5% (Stangier et al. 2007), which is very low. Therefore, we consider that dabigatran shows marked differences in efficiency between individuals. There is a report showing the association between individual differences and APTT (van Ryn et al. 2010). The distribution of APTT after dabigatran administration is normal at around 35–40 s in twice-daily dosing at 50 mg, around 40–48 s in twice-daily dosing at 150 mg, and around 48–64 s in twice-daily dosing at 300 mg. That is, we consider that APTT is widely distributed around the average in the case of dabigatran administration. In addition, Nagasawa et al. (2012) also reported renal dysfunction as a factor for APTT prolongation. Dabigatran is a drug subjected to renal excretion because approximately 80% of it is excreted by the kidneys. Therefore, if dabigatran is administered to patients with renal dysfunction, it accumulates and shows enhanced activity. As a result APTT may be prolonged. Therefore, we also investigated in detail renal function as a factor for APTT prolongation in this study. However, the dose/eGFR values were 4.3 ± 1.5 mg/mL/min in the prolonged-APTT group and 3.8 ± 0.9 mg/mL/min in the control group, and there was no significant difference between both groups. Therefore, the relationship between APTT prolongation and renal function was not recognized in this study because the administered dose was adjusted according to the renal function of the patients. Therefore, we considered that parameters such as internal time and the time of blood drawing are important when we evaluate APTT after dabigatran administration, and we should consider these parameters for blood drawing in the future.

Secondly, in the blood coagulation cascade, thrombin is produced, and coagulation factors above the intrinsic coagulation pathway are activated by a positive feedback mechanism. Thrombin activity is inhibited by dabigatran, and the positive feedback mechanism is also suppressed; the activations of factors V, VIII, and XI are also suppressed (Ansell 2007). As a result, APTT, which reflects an abnormality in the intrinsic coagulation factor, is prolonged. However, it is considered that there are individual differences in coagulation factors above the intrinsic coagulation pathway activated by a positive feedback mechanism (Paul et al. 1987). Even if thrombin is inhibited equally by a certain blood concentration, the suppression of the positive feedback mechanism by dabigatran differs for each individual. Therefore, as a result, we hypothesize that APTT also differs.

Thirdly, in this study, patients who were treated with combinations of dabigatran and p-glycoprotein inhibitors or proton pump inhibitors were included in both the prolonged group and control group. In the prolonged group and control group, the percentages of patients taking p-glycoprotein inhibitors were 50.0% and 31.9%, and those taking proton pump inhibitors were 70.0% and 55.8%, respectively. The bioavailability of dabigatran increased by 15% when it was used in combination with p-glycoprotein inhibitors (Dansirikul et al. 2012). The contraindications for the combined use of dabigatran with p-glycoprotein inhibitors are specified in the package insert because there is a possibility that the risk of bleeding is increased with increasing blood levels of dabigatran. In addition, there is a possibility that APTT does not prolong because the gastrointestinal absorption rate of dabigatran decreases when used in combination with proton pump inhibitors because dabigatran is absorbed under acidic conditions. Therefore, we hypothesize that the combination of agents that affect dabigatran blood levels is associated with the differences in APTT.

For the interpretation of APTT after dabigatran administration, parameters such as the time of blood drawing, internal time of dabigatran, individual variability, and blood concentration

should be evaluated carefully. However, in actual clinical practice, we considered that it is difficult to measure APTT while considering these parameters strictly. Therefore, we consider that it is not easy to identify the cause of the prolonged APTT. In addition, even if APTT does not prolong, it is unclear whether safety is maintained. In view of these points, we consider that APTT as an index of bleeding after dabigatran administration should be carefully examined.

APTT is an indication of the clotting activity of all the intrinsic coagulation factors. APTT shows the correlation between blood levels of dabigatran. However, it has been reported that it is inferior in terms of linearity and reproducibility (Hawes et al. 2013). We consider that what we really want to know is the clotting activity of direct thrombin. In that sense, we hypothesize that there is a possibility that ecarin clotting time, thrombin time, and hemoclot thrombin inhibitor, which is correlated with blood levels of dabigatran, are good indicators (Douxfils et al. 2012). Major bleeding is one of the most important concerns regarding the use of an anti-clotting agent. We consider that indicators for determining the excessive dosage of a drug are essential when major bleeding occurs. However, clinically, these indicators are not widely used at present. We expect that these coagulation indicators will become widely used in the future. However, APTT is most frequently used at the moment. Therefore, we consider that the interpretation of APTT will remain an issue in the future.

4. Experimental

Currently, an accurate baseline for APTT after dabigatran administration has not yet been established. Therefore, in this study, we defined the group whose APTT prolonged to more than 65 s(twice the normal value) after dabigatran administration as the prolonged-APTT group.We defined the group with an APTT of less than 65 s after dabigatran administration as the control group. We analyzed the patients' background features and laboratory data of both groups.

The factors examined aspatients' background features were sex, age, weight, BMI, primary disease (e.g., heart failure, hypertension, dyslipidemia, diabetes mellitus, stroke, TIA), $CHADS_2$ scores, initial doses, bleeding after dabigatran administration, combination of dabigatran with drugs [e.g., antiplatelet drugs,p-glycoprotein inhibitors (verapamil, amiodarone, cyclosporine, tacrolimus, clarithromycin, ritonavir, saquinavir mesilate, nelfinavir mesilate), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole sodium, esomeprazole magnesium)], history of gastrointestinal bleeding, switching from warfarin to dabigatran, and switching from antiplatelet agents to dabigatran.

The laboratory data included the levels of AST, ALT,γ-GT, BUN, Scr, eGFR, CCr, dose/eGFR, dose/CCr,T-Cho, HDL-C, LDL-C, TG, CRP, TP, Alb, RBCs, Hb, Hct, HbA1c, BNP,SBP, and DBP.Data were collected immediately after dabigatran administration.

4.1. Subjects

We recruited the patients who met the following criteria as subjects of this study: (1) outpatients and inpatients of the Department of Cardiovascular Medicine of Yokosuka Kyousai Hospital from March 2011 to July 2013, (2) patients with nonvalvular atrial fibrillation who were administered dabigatran for the purpose of primary or secondary cerebral infarction prevention, and (3) patients whose APTT was measured 3–6 h after dabigatran administration. There were 130 patients (prolonged-APTT group: 120; control group: 10) who met these criteria. This study complied with the Declaration of Helsinki andthe "Ethical Guidelines for Clinical Research."

4.2. Statistical analysis

We compared the prolonged group with the control group in terms of patients' background and laboratory data. The results are presented as mean ± standard deviation (S.D.). We performed the normality test to compare the data volume between the two groups. We used Student's t-test after we confirmed that the data showed a normal distribution. We used the Mann–Whitney U-test when the data did not show a normal distribution. We used the χ^2 test or Fisher's exact test to compare the categorical data. The significance level was 5% ($p < 0.05$). In addition, statistical analysis was performed using JMP® (Version 10, SAS Institute Inc., Cary, NC, USA).

4.3. Ethical regulation

This study was approved by the Yokosuka Kyousai Hospital ethics committee (Approval number: 13-07). This was a retrospective study using medical records. There is no disadvantage to the individual.

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