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Original Article

Influence of proton pump inhibitors on blood dabigatran concentrations in Japanese patients with non-valvular atrial fibrillation

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ABSTRACT

Background: Dabigatran is a direct thrombin inhibitor used to decrease the risk of ischemic stroke in patients with non-valvular atrial fibrillation (NVAF). Its prodrug, dabigatran etexilate (DE) is often co-administrated with a proton pump inhibitor (PPI) because of its adverse effects on the gastrointestinal tract. Drug-drug interactions between DE and PPIs in daily clinical practice have not been fully elucidated.

Methods: Changes in blood dabigatran concentration (DC) were investigated using the dilute thrombin time test in a randomized, open-label, two-period crossover study including 34 Japanese patients with NVAF receiving dabigatran therapy with or without PPI.

Results: The average trough DC was significantly higher without PPI than with PPI (83 ± 42.3 *vs.* 55.5 ± 24.6 ng/mL, respectively; $P < 0.001$). Similarly, the average peak DC was significantly higher without PPI than with PPI (184.1 ± 107.7 *vs.* 124 ± 59.2 ng/mL, respectively; $P = 0.0029$). The average ratio of DC change at the trough and peak levels did not differ significantly among the three PPI types.

Conclusions: PPI administration significantly decreased the trough and peak DCs in patients with NVAF. Therefore, when prescribing PPIs for patients with NVAF in a clinical setting, the possibility that the bioavailability of dabigatran may decrease should be considered.

1. Introduction

Dabigatran is a direct thrombin inhibitor that has been used to decrease the risk of ischemic stroke in patients with non-valvular atrial fibrillation (NVAF) and for direct-current cardioversion and ablation of AF [1–3]. Since dabigatran is not absorbed orally, its prodrug, dabigatran etexilate (DE), which is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis, is often used [4]. Similar to other non-vitamin K oral anticoagulants, routine biological monitoring is not usually required in patients receiving dabigatran therapy owing to its predictable pharmacokinetics with limited drug-drug interactions [1]. However, monitoring of the anticoagulant activity might be useful in certain clinical settings [5]. The dilute thrombin time test was reported to show a high degree of linearity at blood dabigatran concentrations (DC) > 50 ng/mL and was useful for quantitation across the entire on-therapy range [5,6]. The activated partial thromboplastin time (aPTT) is relatively insensitive because the curvilinear response at higher drug levels does not permit accurate quantitation [5]. DE is often co-administered with a proton pump inhibitor (PPI) because of its adverse effects on the gastrointestinal tract [1,7]. It is known that co-administration of PPI may affect the absorption of DE by raising the gastric pH because an acidic environment is required for the dissolution of DE [8,9]. However, drug-drug interactions between DE and PPI have not been fully elucidated in daily clinical practice. Therefore, the changes in DC were examined in Japanese patients with NVAF receiving dabigatran therapy with or without PPI, using the dilute thrombin time test.

2. Material and methods

2.1. Subjects

This randomized, open-label, two-period crossover study including Japanese patients with NVAF was conducted at Tosei General

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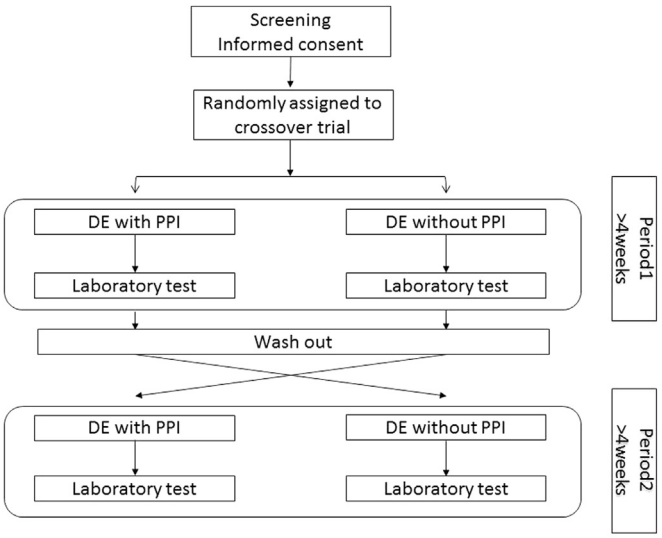

Fig. 1. Schematic study design. DE, dabigatran etexilate; PPI, proton pump inhibitor.

Hospital, Aichi, Japan. From May 1, 2015 to July 31, 2015, 37 patients with NVAF were enrolled and assigned randomly to one of two groups, administration of DE with PPI and administration of DE without PPI. Patients with renal insufficiency (creatinine clearance $<$ 30 mL/min) or peptic ulcer were excluded. Each group crossed over, and blood samples at the trough and peak times were obtained during each period more than 4 weeks after the start of treatment, which was preceded by a 2-week wash-out period (Fig. 1). The trough time was defined as the time immediately before the administration of DE, and the peak time was defined as 2 h after the administration of DE [10].

The PPI selected by the treating physician (lansoprazole [30 mg], rabeprazole [20 mg], or esomeprazole [20 mg]) was used once daily. Creatinine clearance was determined using the Cockcroft-Gault formula [11]. We obtained written, informed consents from all patients. This study was approved by the Ethics Committees of Tosei General Hospital on April 20, 2015 (approval number: 15-03).

2.2. Measurement of DC and aPTT

DC at the trough and peak times was calculated using HemosIL® direct thrombin inhibitor assay (Instrumentation Laboratory, Bedford, MA, USA). This assay is a dilute thrombin time test, which is based on the reaction between dabigatran and exogenous thrombin added to the diluted patient plasma. The associated clotting time was measured using the ACL TOP hemostasis testing system (Instrumentation Laboratory), and then the concentration of dabigatran was estimated from the reference curve of the known plasma standard of dabigatran using HemosIL® dabigatran calibrators (Instrumentation Laboratory). The trough or peak ΔDC ratio was defined as the trough or peak DC in the period without PPI minus the corresponding DC in the period with PPI divided by the trough or peak DC in the period with PPI. Trough and peak aPTTs were measured using HemosIL® APTT-SP (Instrumentation Laboratory).

2.3. Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as means ± standard deviation. Student's *t*-test was used to compare parameters between groups. Kruskal-Wallis test was used to compare the trough and peak ΔDC ratios among the three PPI types. All statistical analyses were performed using the Ekuseru-Tokei statistical software program (Ekuseru-Tokei 2010, Social Survey Research Information Co, Tokyo, Japan).

Table 1
Patients' characteristics.

Patients, *n*	34
Male, *n* (%)	25 (73.5)
Age, years	71.5 ± 9.7
Body Weight, kg	63.7 ± 9.2
Serum creatinine, mg/dL	0.94 ± 0.34
Mean creatinine clearance, mL/min	65.7 ± 19.8
Dose of dabigatran	
110 mg twice daily, *n* (%)	22 (64.7)
150 mg twice daily, *n* (%)	12 (35.3)
CHADS2 score	2.6 ± 1.4
Paroxysmal atrial fibrillation, n (%)	13 (38.2)
Type of proton pump inhibitor	
Lansoprazole, *n* (%)	14 (41.2)
Rabeprazole, *n* (%)	14 (41.2)
Esomeprazole, *n* (%)	6 (17.6)

3. Results

A total of 37 patients with NVAF were enrolled in this study. Two patients dropped out during the first period because of adverse effects. One patient had indigestion and the other had bloody phlegm; both patients were treated with DE + PPI. Furthermore, one patient had acute arterial embolism in the lower limb during the second period of co-administration with PPI. Therefore, results of the remaining 34 patients who completed the entire study were included in the analysis. The characteristics of these 34 patients are presented in Table 1. The average trough DC was significantly higher during the DE without PPI period than during the DE with PPI period (83 ± 42.3 *vs.* 55.5 ± 24.6 ng/mL, respectively; $P < 0.001$) (Fig. 2A). Similarly, the average peak DC was significantly higher during the DE without PPI period than during the DE with PPI period (184.1 ± 107.7 *vs.* 124 ± 59.2 ng/mL, respectively; $P = 0.0029$) (Fig. 2B). The peak DC was significantly higher than the trough DC during both periods (Fig. 3). The trough and peak DCs with and without co-administration of the three PPI types are presented in Fig. 4A and B, respectively. The average trough and peak ΔDC ratio did not differ significantly among the three PPI types (Table 2). Similar to the results of the dilute thrombin time test, the average trough aPTT was significantly higher during the period without PPI than during the period with PPI (43.7 ± 6.1 *vs.* 39 ± 4.6 s, respectively; $P < 0.001$). In addition, the average peak aPTT was significantly higher during the period without PPI than during the period with PPI (56.9 ± 13.5 *vs.* 48.6 ± 8.8 s, respectively; $P = 0.0028$). The average control value of aPTT was 30.1 ± 0.5 s.

4. Discussion

To the best of our knowledge, this is the first randomized, crossover study on the drug-drug interactions between DE and PPIs in patients with NVAF. In this study, co-administration of PPIs significantly decreased DC at both the trough and peak times.

Results of the RE-LY trial showed that patients cotreated with a PPI exhibited a 12.5% decrease in the area under the plasma concentration-time curve at steady state [8]. Similarly, co-administration of pantoprazole decreased the area under the plasma concentration-time curve and the maximum plasma concentration at steady state

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