Distribution of Anti-Factor Xa Activity in Patients on Edoxaban Therapy for Non-Valvular Atrial Fibrillation

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Circulation Journal 2016; 80: 745 – 747

**Background:** The distribution of anti-factor Xa activity (AXA) values in non-valvular atrial fibrillation (NVAF) patients on edoxaban therapy has not been fully elucidated.

**Methods and Results:** The steady-state trough and peak AXA values were measured in 66 NVAF patients. The trough AXA value did not differ significantly between the 60-mg and the 30-mg OD groups (0.17±0.13 IU/ml vs. 0.12±0.11 IU/ml, respectively; P=0.17). Similarly, the peak AXA value did not differ significantly between the 2 groups (1.45±0.81 IU/ml vs. 1.25±0.48 IU/ml, respectively; P=0.26).

**Conclusions:** Recommended dosing should be followed for sufficient efficacy of edoxaban. (Circ J 2016; 80: 745–747)

**Key Words:** Anti-factor Xa activity; Atrial fibrillation; Edoxaban

Edoxaban is a selective factor-Xa (FXa) inhibitor recently approved for use in Japan for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF).1–3 The typical recommended dosage of edoxaban is 60 mg once daily (OD), but 30 mg OD is recommended for patients with the following conditions: body weight ≤60 kg, creatinine clearance ≤50 ml/min or concomitant use of a medication with P-glycoprotein interaction.1 Chromogenic anti-factor Xa activity (AXA) is the most appropriate assay to measure the pharmacodynamics of a FXa inhibitor and to estimate plasma drug concentrations.4–7 However, the distribution of AXA values in NVAF patients receiving edoxaban has not been fully elucidated in daily clinical practice. Therefore, the aims of the present study were to determine the distribution of the steady-state trough and peak AXA values in Japanese NVAF patients receiving edoxaban.

**Methods**

**Study Design and Subjects**

This observational study of Japanese patients with NVAF on edoxaban therapy was conducted during routine clinical practice at Tosei General Hospital, Aichi, Japan. From January 1, 2015 to June 30, 2015, 66 patients were started on edoxaban and considered for study entry. Patients provided written informed consent to participate, and this study was conducted in accordance with the ethical policies of Tosei General Hospital. Creatinine clearance was determined by the Cockcroft-Gault formula.8

**Measuring AXA**

The HemosIL Liquid Heparin Kit (Instrumentation Laboratory, Lexington, KY, USA) was used for measuring AXA as previously reported.6,9 AXA values at trough and peak times after repeated edoxaban intake were measured >72 h after the start of treatment. The trough time was defined as that immediately before the intake of edoxaban, and the peak time was defined as 2 h after the intake of edoxaban.

**Statistical Analysis**

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean±standard deviation. To compare parameters between groups, unpaired t-test and chi-square test was used. To compare AXA values, the Mann-Whitney U test and the Wilcoxon signed-rank test were used. To evaluate the factors affecting trough and peak AXA values, multiple regression analysis was performed. P<0.05 was considered to indicate statistical significance. All statistical analyses were conducted with the Ekuseru-Tokei statistical software program (Ekuseru-Tokei 2010, Social Survey Research Information Co, Tokyo, Japan).

**Results**

**Patients Characteristics**

The characteristics of the patients are shown in the Table: 17
patients received edoxaban 60 mg OD, and 49 patients received 30 mg OD, consistent with the recommendation.1

**AXA Values**

Steady-state AXA values were compared between the 60-mg OD group and the 30-mg OD group (Figure). The trough AXA value did not significantly differ between the groups (0.17±0.13 vs. 0.12±0.11 IU/ml, respectively; P=0.17). Similarly, the peak AXA value did not significantly differ between groups (1.45±0.81 vs. 1.25±0.48 IU/ml, respectively; P=0.26). Furthermore,

### Table. Characteristics of Patients on Edoxaban Therapy for Non-Valvular Atrial Fibrillation

| Characteristic                                      | 60 mg once daily (n=17) | 30 mg once daily (n=49) | P value |
|-----------------------------------------------------|-------------------------|-------------------------|---------|
| Age (years)                                         | 68.8±9.6                | 78.5±6.9                | <0.01   |
| Male sex, n (%)                                     | 13 (76.5)               | 24 (49.0)               | <0.05   |
| Body weight (kg)                                    | 72.4±16.4               | 52.0±8.9                | <0.01   |
| Paroxysmal atrial fibrillation, n (%)               | 10 (65.8)               | 22 (44.9)               | 0.32    |
| Serum creatinine (mg/dl)                            | 0.98±0.22               | 1.05±0.48               | 0.58    |
| Mean creatinine clearance (ml/min)                  | 72.0±18.8               | 44.7±16.7               | <0.01   |
| Mean CHADS2 score                                    | 1.8±1.2                 | 2.2±1.1                 | 0.20    |
| 0, n (%)                                            | 2 (11.8)                | 2 (4.1)                 | 0.25    |
| 1, n (%)                                            | 4 (23.5)                | 10 (20.4)               | 0.79    |
| 2, n (%)                                            | 8 (47.1)                | 21 (42.9)               | 0.76    |
| ≥3, n (%)                                           | 3 (17.6)                | 16 (32.7)               | 0.24    |
| Congestive heart failure, n (%)                     | 8 (47.1)                | 23 (46.9)               | 0.98    |
| Hypertension, n (%)                                 | 11 (64.7)               | 29 (59.2)               | 0.69    |
| Age ≥75 years, n (%)                                | 4 (23.5)                | 36 (73.5)               | <0.01   |
| Diabetes mellitus, n (%)                            | 7 (41.2)                | 10 (20.4)               | 0.09    |
| Baseline stroke/transient ischemic attack/systemic embolism, n (%) | 2 (11.8) | 5 (10.2) | 0.86 |
| Previous anticoagulants                              |                         |                         |         |
| None, n (%)                                         | 10 (65.8)               | 24 (50.0)               | 0.48    |
| Warfarin, n (%)                                     | 4 (23.5)                | 20 (40.8)               | 0.20    |
| Dabigatran, n (%)                                   | 1 (5.9)                 | 2 (4.1)                 | 0.76    |
| Rivaroxaban, n (%)                                  | 2 (11.8)                | 2 (4.1)                 | 0.25    |
| Apixaban                                            | 0 (0.0)                 | 1 (2.0)                 | 0.55    |

**Figure.** Distribution of steady-state trough and peak anti-factor Xa activity (AXA) values of the 60-mg once daily (OD) group and the 30-mg OD group. Neither the trough nor the peak AXA values were significantly different between groups. The peak AXA values are significantly higher than the trough AXA values in both groups. Horizontal lines in boxes represent medians. Tops and bottoms of boxes indicate 75th and 25th percentile, respectively. Tops and bottoms of bars indicate maximum and minimum non-outliers, respectively. X indicates outliers above or below 1.5-fold the interquartile range from the 75th and 25th percentiles.
the peak AXA values were significantly higher than the trough AXA values in both groups. High dose, body weight and serum creatinine were significantly related to trough AXA values ($β=0.536$, $P=0.001$, $β=0.443$, $P=0.005$ and $β=0.506$, $P=0.001$, respectively), but female sex and age were not ($β=0.059$, $P=0.622$ and $β=0.145$, $P=0.270$, respectively). High dose, female sex and serum creatinine were significantly related to peak AXA values ($β=0.358$, $P=0.029$, $β=0.324$, $P=0.014$ and $β=0.322$, $P=0.014$, respectively), but age and body weight were not ($β=−0.146$, $P=0.299$ and $β=−0.277$, $P=0.095$, respectively).

**Discussion**

To the best of our knowledge, this is the first report of the distribution of steady-state AXA values in Japanese NVAF patients on edoxaban therapy in daily clinical practice. Though routine and frequent monitoring of the AXA values is not recommended in edoxaban therapy, a sensitive biomarker may be useful in certain situations, such as in patients with acute thromboembolism or bleeding, or in those who require emergency surgery or other invasive procedure. Chromogenic AXA assays are reported as the most appropriate for measuring the pharmacodynamics of FXa inhibitors, including edoxaban. Therefore, we aimed to elucidate the steady-state AXA values in Japanese NVAF patients receiving edoxaban, according to dose. The AXA values increased significantly and were approximately 8- to 10-fold from trough to peak at steady-state in both treatment groups. The anti-FXa effect of edoxaban was minimal but definitely remained at trough, as the baseline AXA values were at 0IU/ml for all 34 patients who were not previously prescribed an anticoagulant. Further, the trough and peak AXA values did not differ significantly between the groups. This result suggested that no significantly different anticoagulant effect should be expected, provided the recommended dosing is used. However, further research is required to determine whether monitoring of AXA values can improve the efficacy and safety outcomes for patients on edoxaban therapy.

**Study Limitations**

First, this study was performed at a single institution with a limited number of subjects. Second, the peak time was defined as 2h after drug administration according to a previous report, but the actual peak concentration may differ among individual patients. Third, the different chromogenic AXA assays available on the market may show different relationships with plasma edoxaban concentrations depending on the reagent, so the results of this study might be different had other reagents been used.

In summary, the distribution of AXA values among Japanese patients with NVAF and who were taking edoxaban in daily clinical practice was investigated at steady state. We conclude that the peak AXA values were significantly higher than the trough AXA values in both the 60-mg OD group and the 30-mg OD group and that the trough and peak AXA values did not differ significantly between the 2 groups, suggesting that the recommended dosing should be kept to get sufficient efficacy of edoxaban.

**Disclosures**

H.O. and M.A. have received lecture fees from Bristol-Myers Squibb, Pfizer, Bayer Yakuhin Ltd, Boehringer Ingelheim, and Daiichi Sankyo.

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