Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis

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Summary

Edoxaban is an oral, direct, once-daily, factor Xa inhibitor developed for stroke prevention in patients with atrial fibrillation and for the treatment and secondary prevention of recurrent thromboembolism in patients with acute symptomatic venous thromboembolism. Among elderly patients who require anticoagulation therapies, some may have end-stage renal disease (ESRD). This open-label, phase 1, randomised, two-way crossover study was conducted to evaluate the pharmacokinetics of edoxaban in 10 subjects on haemodialysis. Eligible subjects with ESRD on chronic haemodialysis received a single, oral dose of edoxaban 15 mg 2 hours (h) prior to (on-dialysis) or in between (off-dialysis) haemodialysis sessions. Haemodialysis resulted in a minor decrease in mean total exposure (AUC∞, 676.2 ng·h/ml) as compared with that observed in subjects off-dialysis (691.7 ng·h/ml). Mean maximum observed plasma concentration (Cmax) values were comparable between on-dialysis and off-dialysis treatments (53.3 vs 56.3 ng/ml, respectively). Mean apparent total body clearance (CL/F) values were 24.1 and 22.5 l/h during the on-dialysis and off-dialysis treatment periods, respectively. Dialyser clearance was 5.7 l/h and haemodialysis clearance was 6.1 l/h. Haemodialysis clearance was only 6.1 l/h, suggesting that it only accounts for one-fourth of the total clearance in these subjects. A single, oral dose of 15 mg of edoxaban was well tolerated by subjects with ESRD. In conclusion, based on these single-dose PK data, a supplementary dose of edoxaban may not be required following a haemodialysis session. Importantly, haemodialysis is not an effective mechanism for removal of edoxaban from the blood.

Keywords

Edoxaban, haemodialysis, pharmacokinetics, oral factor Xa inhibitor, elimination

Introduction

Renal impairment results in increased systemic exposure of drugs and metabolites for which renal clearance is a major route of elimination. In subjects with end-stage renal disease (ESRD), in addition to affecting renal clearance, renal impairment may also affect protein binding and nonrenal clearance (1). Subjects undergoing haemodialysis may see a decrease in drug exposure if the drug is cleared through this procedure, resulting in ineffective therapy (2). Depending upon the extent to which a drug is cleared by dialysis, subjects may need a supplemental dose when undergoing haemodialysis (3).

Edoxaban is an oral, direct, once-daily, factor Xa (FXa) inhibitor (4) approved in the United States for the prevention of stroke in patients with atrial fibrillation (AF) with creatinine clearance >95 and for the treatment and secondary prevention of recurrent thromboembolism in patients with acute symptomatic venous thromboembolism (5, 6). In healthy subjects, oral bioavailability is 62 % of an administered dose of edoxaban, of which renal and nonrenal routes are equally accountable for clearance of the absorbed drug (7, 8). Nonrenal clearance includes biliary secretion of unchanged drug and metabolism. Edoxaban is metabolised by carboxylesterase 1 to M-4, a human-specific metabolite, which constitutes <10% of total edoxaban exposure. M-4 is pharmacologically active with anticoagulant activity similar to that of the parent drug. Cytochrome P450 3A4 (CYP3A4) is involved in the formation of three metabolites: M-5, M-6, and M-8; the latter two have anticoagulant activity. Pharmacokinetic (PK) analyses of the metabolites show that the plasma metabolite concentrations follow the time course of the parent drug, although at much lower plasma concentrations. M-4 is the most abundant metabolite (approximately 9%). Metabolites can be detected in urine (5%) and faeces (4%) (8).

Patients requiring anticoagulants tend to be older in age (9, 10) and may have age-related reductions in renal function (11). Edoxaban has been previously evaluated in subjects with mild, moderate, and severe renal impairment, as well as in ESRD subjects treated with continuous ambulatory peritoneal dialysis (12). Impaired renal function has been shown to reduce the clearance of edoxaban, leading to increased exposure. Modelling and
simulation analyses, based on data from a phase 2 dose-finding study in AF patients, demonstrated that an increase in edoxaban exposure results in an increase of the risk of bleeding (13). As such, a dose reduction was incorporated into edoxaban phase 3 study designs for subjects with moderate renal impairment (creatinine clearance [CLcr] 30–50 ml/minute [min]) (5, 6). The primary objective of this study was to evaluate the effect of haemodialysis on the exposure of edoxaban in subjects with ESRD following the administration of a single, oral dose of edoxaban 15 mg.

Methods

Study design

This was a phase 1, single-centre, open-label, randomised, two-treatment, two-period, two-way crossover study in subjects with ESRD to evaluate the effect of haemodialysis after a single, oral dose of edoxaban 15 mg. Subjects received a single, oral dose of edoxaban 15 mg on two occasions: on-dialysis they received a single, oral, 15-mg dose of edoxaban 2 hours (h) before a 4-h haemodialysis session; and off-dialysis they received a single, oral, 15-mg dose of edoxaban between haemodialysis sessions. Subjects were randomised to 1 of the following two treatment sequences: sequence 1) on-dialysis dose of edoxaban, ≥7 days washout, off-dialysis dose of edoxaban; sequence 2) off-dialysis dose of edoxaban, ≥7 days washout, on-dialysis dose of edoxaban (▶Figure 1). The 15-mg once-daily dose of edoxaban was chosen because it has been previously studied in patients with ESRD and was well tolerated (12).

This study was approved by an institutional review board and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline E6 for Good Clinical Practice (GCP), appropriate components of the US Food and Drug Administration GCP regulations, and the Health Insurance Portability and Accountability Act.

Selection of subjects

Subjects were eligible to enroll if they were 18 to 65 years of age, had a body mass index of 18 to 40 kg/m², and a negative faecal occult blood test. All subjects were required to have ESRD and to have been maintained on stable regimens of haemodialysis three times a week for ≥3 months prior to screening. Exclusion criteria included, but were not limited to, a history of relevant drug sensitivity or major bleeding, major trauma or major surgical procedure of any type within six months before the first dose of edoxaban, peptic ulcer or gastrointestinal bleeding, or use of any drugs or substances known to be strong inhibitors or strong inducers of
CYP3A4/5 enzymes or P-glycoprotein (P-gp) within four weeks prior to the first dose of edoxaban. All subjects provided written informed consent prior to study participation, including any protocol-specific screening procedures or administration of study drug.

**Haemodialysis methods**

Haemodialysis treatments were 4 h in duration, and were conducted with a Fresenius F180 NR high flux dialyzer (Waltham, MA, USA) and sodium bicarbonate-based dialysate. A polysulfone synthetic membrane with a surface area of 1.8 m² was used with a fixed dialysate flow rate of 500 ml/minute (min). Targeted blood flow rates were 350 ml/min in treatment A and B, but varied between subjects depending on their vascular access.

**Study assessments**

For all subjects, blood samples for the analysis of edoxaban plasma concentrations, the active metabolite M-4, and the minor metabolites M-1, M-8, and M-6 were collected within approximately 1 h prior to dosing and at the following times post edoxaban dose: 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, and 48 h. During dialysis (i.e. 2.5, 3, 4, 5, and 6 h for the on-dialysis treatment), blood samples were collected from the afferent blood line of the dialyser. During the on-dialysis treatment period, additional blood samples were taken for analysis of plasma concentrations of edoxaban and M-4 from the efferent blood line of the dialyzer at 2.5, 3, 4, 5, and 6 h post edoxaban dose.

In addition, during the on-dialysis treatment period, each subject’s dialysate was collected before the start of the haemodialysis procedure and throughout the haemodialysis session (2–3, 3–4, 4–5, and 5–6 h post edoxaban dose). Dialysate volume for each interval was measured. Blood flow from the afferent blood line of the dialyzer was recorded, as was the dialyzer effluent flow rate. Blood samples for plasma protein binding measurement were obtained for all subjects at 2 and 6 h postdose. For subjects on dialysis, the 2-h sample was taken immediately prior to the start of dialysis, and the 6-h sample was taken immediately after the end of dialysis.

**Bioanalysis**

The plasma concentrations of edoxaban and its metabolites were analyzed by Advion BioServices (Ithaca, NY, USA) using two validated liquid chromatography separation and tandem mass spectrometry detection (LC-MS/MS).

The first method measures free-base edoxaban and M-4 simultaneously in human plasma, with calibration ranges of 0.764 to 382 ng/ml and 0.0792 to 7.92 ng/ml, respectively. The analytes and deuterium-labelled internal standards (one for each analyte) were isolated from 200-µl plasma sample using Oasis MCX™ (mixed-mode cation exchange resin) 96-well solid-phase extraction plate. Extracted samples were injected into a gradient chromatograph, using 5 mM ammonium acetate (pH 7.0) as mobile phase A and methanol as mobile phase B, at a flow rate of 0.3 ml/min. The mobile phase B, at a flow rate of 0.3 ml/min. The flow rate was 0.3 ml/min. The eluted analytes and internal standards were detected by an API4000 mass spectrometer with TurboSpray source (positive ionization mode; AB Sciex, Framingham, MA, USA). Edoxaban and M-4 were quantified using quadratic (1/X² weighting) and linear (1/X² weighting) calibration curves, respectively.

The second method measures free-base M-1, M-6, and M-8 simultaneously in human plasma with a calibration range of 0.1 to 5.0 ng/ml for each analyte. Plasma samples (300 µl) were mixed with deuterated internal standards (one for each analyte), pH adjusted (addition of 2% formic acid, 200 µl), centrifuged, and loaded into a 96-well, solid-phase extraction block (MCX™, 10 mg). Extracted samples were injected into a gradient chromatograph (mobile phase A: 5 mM ammonium acetate buffer at pH 7, mobile phase B: methanol) with a reverse phase column (Zorbax Eclipse XDB-Phenyl, 50 mm × 2.1 mm internal diameter, 5 µm).

The flow rate was 0.3 ml/min. The eluted analytes and internal standards were detected by an API4000 mass spectrometer equipped with TurbolonSpray source (positive ionization mode). All analytes were quantified using linear (1/X² weighting) calibration curves.

**Pharmacokinetic (PK) analysis**

The following PK parameters were calculated, as appropriate, from the individual plasma concentrations of edoxaban and associated metabolites using a noncompartmental approach: the area under the plasma concentration vs time curve (AUC) from time 0 to the last measurable concentration (AUClast), AUC from the time of dosing extrapolated to infinity (AUC∞), maximum observed plasma concentration (Cmax), plasma drug concentration at 24 h

<table>
<thead>
<tr>
<th>Trait</th>
<th>Sequence 1 (N=6)</th>
<th>Sequence 2 (N=4)</th>
<th>Overall (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (50.0)</td>
<td>4 (100.0)</td>
<td>7 (70.0)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (50.0)</td>
<td>0 (0.0)</td>
<td>3 (30.0)</td>
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<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Black</td>
<td>3 (50.0)</td>
<td>2 (50.0)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>White</td>
<td>2 (33.3)</td>
<td>2 (50.0)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>Median (min–max)</td>
<td>48.0 (37–63)</td>
<td>46.0 (42–50)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Median (min–max)</td>
<td>26.9 (22.7–36.1)</td>
<td>29.9 (25.0–32.5)</td>
</tr>
</tbody>
</table>

Sequence 1: on-dialysis treatment followed by off-dialysis treatment. Sequence 2: off-dialysis treatment followed by on-dialysis treatment. BMI, body mass index; SD, standard deviation.
(C₂₄₀), time of maximum observed plasma concentration (tₘₐₓ), apparent total body clearance (CL/F), apparent volume of distribution (Vₛ/F), and metabolite-to-parent ratio for AUCₜₘₙₙ (MPR). For subjects on dialysis, the following PK parameters were also calculated, as appropriate, from the individual dialysate concentrations of edoxaban and M-4 collected from the afferent and efferent lines of the dialyser: AUC from 2 to 6 h post edoxaban dose from the afferent line of the dialyzer (AUCₐ₂­₆ₜ), AUC from 2 to 6 h post edoxaban dose from the efferent line of the dialyser (AUCₑ₂­₆ₜ), the amount of edoxaban recovered in the dialysate from time t to time t’ (A₁₂₅₉), the total amount of edoxaban recovered in the dialysate (A₅₀₉), and edoxaban haemodialysis clearance (CLₑ). Pharmacokinetic parameters were computed using WinNonlin Professional (Version 5.2; Pharsight; St. Louis, MO, USA) or SAS® on SAS Drug Development platform (SASDD v.3.4, SAS 9.1.3 on UNIX).

### Safety

All adverse events (AEs), whether observed by the investigator or reported by the subject, were recorded up to 30 days following edoxaban dosing. Additional safety variables included physical exams, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory assessments.

All premature study discontinuations were recorded. Following randomisation, subjects may have been withdrawn for any of the following reasons: AE, lost to follow-up, death, protocol violation, subject-withdrawn consent, or study termination by the sponsor. If the subject was withdrawn due to an AE, the investigator followed the subject until the AE had resolved or stabilised.

### Statistical analyses

Demographic and other baseline characteristics were summarised by treatment sequence group (sequence 1 and sequence 2) using descriptive statistics for the randomized analysis set. The randomised analysis set comprised all subjects who signed informed consent and were randomised into the study.

All PK concentrations and parameters were summarised by treatment (on-dialysis or off-dialysis) using descriptive statistics for the PK analysis set, which included all subjects who received ≥1 dose of edoxaban and had an evaluable PK profile. A mixed-effect analysis of variance model with treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect was performed on the ln-transformed AUCₜₘₙₙ (and AUC₀₋₀ and Cₘₐₓ as secondary endpoints) for edoxaban obtained from both the on-dialysis treatment and off-dialysis treatment. The resulting point estimates (geometric least squares means [LSM]), their ratios (on-dialysis/off-dialysis), and 90% confidence intervals (CIs) for the ratios were presented.

Nonparametric statistical analyses using the Wilcoxon rank sum statistic, with Hodges-Lehmann estimator of differences and distribution-free 90% CI based on the Moses method, were performed for tₘₐₓ and terminal half-life (t½ₑ) of edoxaban. The comparisons of interest were on-dialysis treatment vs off-dialysis treatment. The remaining PK parameters for edoxaban were summarised only with descriptive statistics. Descriptive statistics were performed for metabolite/parent ratios of AUCs and Cₘₐₓ as well as the PK parameters of metabolites M-4, M-1, M-8, and M-6.

![Mean edoxaban plasma concentrations over time](image-url)

**Figure 2:** Mean edoxaban plasma concentrations over time. Error bars = standard deviation.
All safety data were summarised by treatment group for the safety analysis set, which included all subjects who received ≥1 dose of edoxaban and had ≥1 safety assessment. No inferential or comparative statistics were performed for safety data.

It was determined that eight subjects (4 in each treatment sequence) would be sufficient to provide a reliable estimate for the ratio of mean AUC values calculated on- and off-dialysis. However, the number of subjects was not based on a formal sample size calculation. A total of 10 subjects were enrolled to compensate for potential dropouts.

**Results**

**Subjects**

A total of 10 subjects with ESRD were enrolled in the study and randomised to treatment. The aetiologies of the ESRD were hypertensive nephrosclerosis (8 subjects) and diabetic nephropathy (2 subjects). Nine subjects completed the study. One subject (sequence 1) dropped from the study due to a family emergency and completed only period 1 (on-dialysis treatment) (Figure 1). Subject demographics and baseline characteristics can be found in Table 1. All 10 subjects were included in all analysis sets.

**Edoxaban pharmacokinetics**

Overall, peak mean plasma concentrations of edoxaban occurred at 2 h post edoxaban dose following on-dialysis and off-dialysis treatment (Figure 2). Mean plasma concentrations were slightly lower over the 1- to-6-h post edoxaban dose period on-dialysis compared with off-dialysis. From 8 to 48 h following the edoxaban dose, the mean concentration-time profiles for both treatments were nearly superimposable. A summary of the PK parameters of edoxaban following a single, oral, 15-mg dose is presented in Table 2. Haemodialysis resulted in a minor decrease in total exposure as compared with that observed for off-dialysis, with mean AUC₀–∞ values of 676.2 vs 691.7 ng·h/ml, respectively. Mean Cₘₐₓ values were comparable between on-dialysis and off-dialysis treatments (53.3 vs 56.3 ng/ml, respectively). Median tₘₐₓ values increased from 2.0 to 2.3 h for the on-dialysis treatment. Haemodialysis appeared to have a minimal effect on the Cₘₐₓ and tₘₐₓ of edoxaban, which was to be expected as these occurred prior to the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On-dialysis (N=10)</th>
<th>Off-dialysis (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>53.3 ± 15.14</td>
<td>56.3 ± 23.25</td>
</tr>
<tr>
<td>tₘₐₓ (h)</td>
<td>Median (min–max)</td>
<td>2.3 (1.0–5.0)</td>
</tr>
<tr>
<td>AUC₀–∞ (ng·h/mL)</td>
<td>676.2 ± 220.86</td>
<td>691.7 ± 149.84</td>
</tr>
<tr>
<td>tₜ/² (h)</td>
<td>Arithmetic mean ± SD</td>
<td>10.6 ± 3.13</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>Arithmetic mean ± SD</td>
<td>24.1 ± 7.07</td>
</tr>
</tbody>
</table>

AUC₀–∞, area under the curve from the time of dosing extrapolated to infinity; CL/F, apparent total body clearance; Cₘₐₓ, maximum (peak) observed plasma concentration; SD, standard deviation; tₜ/², terminal half-life; tₘₐₓ, time of maximum observed plasma concentration.

[Figure 3: Mean metabolite plasma concentrations over time. A) Metabolite M-4.]
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start of haemodialysis. Haemodialysis appeared to have no effect on \( C_{24} \) with values remaining constant as compared with when subjects were off-dialysis (7.7 vs 7.6 ng/ml, respectively). Median \( t_{1/2} \) decreased slightly from 10.0 to 9.3 h during on-dialysis treatment. Mean \( CL/F \) values were 24.1 and 22.5 l/h during the on-dialysis and off-dialysis treatment periods, respectively (▶ Table 2).

The total exposure of edoxaban was 8.7% lower in subjects on-dialysis than off-dialysis (650.5 and 712.8 ng·h/ml, respectively).

The ratio of geometric LSMeans was slightly lower than 100 (91.3), and the lower limit of the 90% CI of the ratio of geometric LSMeans of the total exposures was outside the 80% to 125% interval (77.9%, 106.9%). The distribution-free 90% CI constructed around the Hodges-Lehmann estimator for the differences in median \( t_{\text{max}} \) and \( t_{1/2} \) indicated that the \( t_{\text{max}} \) and \( t_{1/2} \) values on-dialysis were similar to those obtained off-dialysis.

Dialyser PK results indicated that edoxaban mean AUC_{eff,2–6h} was approximately 1.4 times (27%) lower than mean AUC_{aff,2–6h}.

Figure 3: B) Metabolite M-1. C) Metabolite M-6. Error bars = standard deviation.
(116.9 vs 160.9 ng·h/ml, respectively) and dialyzer clearance (CL_{dial, plasma}) was 94.6 ml/min (5.68 l/h). As haemodialysis clearance (CL_{p}) was only 6.1 ± 0.96 l/h compared with a CL/F of 22.5 ± 4.50 l/h off-dialysis, this finding suggests that haemodialysis clearance only accounts for one-fourth of the total clearance in these subjects. The amount of edoxaban recovered in the dialysate was 0.99 mg, 6.6% of the 15-mg dose administered. The mean percentage of protein bound for edoxaban in plasma on-dialysis and off-dialysis was comparable. Mean percent values on-dialysis were 60.6% and 62.9% at 2 and 6 h post edoxaban dose, respectively. During the off-dialysis treatment period, values were 60.0% and 61.6% at 2 and 6 h post edoxaban dose, respectively.

**Metabolite pharmacokinetics**

Mean plasma concentrations of M-4, M-1, and M-6 were plotted over time for subjects on- and off-dialysis (Figure 3). The majority of plasma concentration measures for M-8 were below the lower limit of quantification; therefore, no PK evaluation was performed for this metabolite. Peak mean plasma concentrations of M-4 occurred at 2 h post edoxaban dose on-dialysis and at 4 h off-dialysis. Mean M-4 plasma concentrations were initially lower over the 2.5- to 6 h post edoxaban dose period for the on-dialysis treatment compared with those obtained off-dialysis, and then greater over the 12- to 48 h postdose interval. Peak mean plasma concentrations of M-1 occurred at 12 and 8 h post edoxaban dose following on-dialysis and off-dialysis treatments, respectively. Mean plasma concentrations of M-1 were lower over the 2- to 24-h post edoxaban dose period for the on-dialysis treatment compared with those obtained during dialysis sessions (off-dialysis). Peak mean plasma concentrations of M-6 occurred at 2 and 3 h post edoxaban dose following on-dialysis and off-dialysis treatments, respectively. Mean plasma concentrations of M-6 were lower over the 1- to 6 h postdose period in subjects on-dialysis compared with subjects off-dialysis, and then slightly greater over 12- to 48-h following the edoxaban dose. There was a high degree of variability in estimates of total exposure for all metabolites. A summary of the remaining PK results of the metabolites can be found in Table 3. Dialyser PK M-4 results showed that mean AUC_{0-12} was approximately 1.5 times (33%) lower than mean AUC_{0-12,ab} (18.7 vs 27.8 ng·h/ml, respectively) and mean dialysis clearance was 4.8 l/h. The mean metabolite/parent ratios for M-4 were 18.6% and 17.5% in the afferent and efferent lines, respectively (data not shown).

**Safety analyses**

There were no deaths, serious AEs, or discontinuations due to AEs in this study. One subject withdrew from the study prior to period 2 due to a family emergency. Only one subject reported a total of 3 treatment-emergent AEs: blurred vision at 11 min after start of dialysis treatment and hypotension and arteriovenous fistula thrombosis 8 h and 3 days, respectively, following off-dialysis treatment. The episode of arteriovenous fistula thrombosis was considered unrelated to study drug. No anticoagulants were administered at the dialysis site with edoxaban treatment. Only the AE of blurred vision was considered related to study drug. Clinical laboratory, vital signs, physical examination, and ECG results remained unaffected during on-dialysis and off-dialysis periods.

**Discussion**

Based on the results of this study, haemodialysis did not significantly remove edoxaban from the blood, as evidenced by similar total exposure on- and off-dialysis. Haemodialysis had a minimal effect on the apparent total body clearance of edoxaban, with CL/F values of 24.1 l/h vs 22.5 l/h on- and off-dialysis, respectively. Haemodialysis clearance of edoxaban was only 5.7 l/h. Based on the single-dose PK data, a supplementary dose of edoxaban may not be required following a haemodialysis session. Furthermore, in cases of overdose or need for removal of edoxaban from the bloodstream, haemodialysis would not serve as an effective tool.

A key finding in this study was the alteration of the metabolite profile for edoxaban. The overall exposure and metabolite/parent

**Table 3: Summary of plasma pharmacokinetics parameters results for edoxaban metabolites.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>M-4</th>
<th>Off-dialysis (N=9)</th>
<th>M-1</th>
<th>Off-dialysis (N=9)</th>
<th>M-6</th>
<th>Off-dialysis (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>9.8 ± 7.05</td>
<td>10.2 ± 4.98</td>
<td>7.6 ± 4.20</td>
<td>10.6 ± 4.45</td>
<td>2.0 ± 1.00</td>
<td>2.3 ± 1.33</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>2.1 (2.0–12.0)</td>
<td>4.0 (2.0–8.0)</td>
<td>12.0 (2.0–36.0)</td>
<td>8.0 (6.0–24.1)</td>
<td>2.3 (2.00–12.0)</td>
<td>5.0 (2.0–6.00)</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng·h/mL)</td>
<td>193.3 ± 255.48</td>
<td>151.9 ± 101.83</td>
<td>176.8 ± 56.07</td>
<td>250.6 ± 67.48</td>
<td>35.0 ± 9.90b</td>
<td>42.4 ± 13.91</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>13.0 ± 4.95</td>
<td>11.3 ± 3.78</td>
<td>14.4 ± 1.46</td>
<td>11.5 ± 0.45</td>
<td>13.2 ± 2.05b</td>
<td>13.1 ± 2.45</td>
</tr>
<tr>
<td>Metabolite to parent ratio: AUC_{0-∞} (%)</td>
<td>25.0 ± 20.81</td>
<td>22.1 ± 13.58</td>
<td>31.1 ± 8.23</td>
<td>37.5 ± 15.54</td>
<td>5.9 ± 2.05</td>
<td>6.2 ± 2.23</td>
</tr>
</tbody>
</table>

Data provided as mean ± standard deviation, except for t_{max}, which is represented by median (min–max). AUC_{0-∞} area under the curve from the time of dosing extrapolated to infinity; C_{max}, maximum (peak) observed plasma concentration; t_{max}, terminal half-life; t_{1/2}, time of maximum observed plasma concentration. aFor M-1, mean values were calculated from 5 and 4 subjects after on-dialysis treatment and off-dialysis treatment, respectively. bN=9. Value is not adjusted for molecular weight.
ratios for the measured metabolites, especially M-4, were much higher in subjects with ESRD (metabolite/parent ratio ~23%) relative to healthy subjects in a previous study (metabolite/parent ratio ~9.0%) (8). These results indicate that when renal clearance (which contributes ~35% to total clearance and 50% of clearance of the absorbed dose) (7, 8) is compromised, clearance through metabolism plays a larger role in the total clearance of edoxaban. Haemodialysis was more effective in the removal of the minor metabolites M-1 and M-6 in comparison to removal of edoxaban or M-4, as evidenced by a decrease in total exposure of M-1 and M-6 in subjects undergoing haemodialysis. Haemodialysis had a minimal effect on the peak or total exposure of the active human-specific metabolite M-4. The metabolite-to-parent ratio for M-4 was similar on-dialysis and off-dialysis. The metabolite-to-parent ratio observed in this study is higher than that observed in subjects with normal renal function (8), suggesting that M-4 clearance is slower in these subjects as compared with those with normal renal function.

The mean percentage of protein bound for edoxaban in plasma was comparable during the on- and off-dialysis treatment periods. Mean percent values on-dialysis were 60.6% and 62.9% at 2 and 6 h post dose, and 60.0% and 61.6% at 2 and 6 h post dose off-dialysis. The protein binding values were similar to previously observed values in healthy subjects (40%–59%) (14), thus, protein binding was not appreciably affected in subjects with ESRD receiving haemodialysis.

Overall, in subjects with renal insufficiency, metabolism contributes to a larger extent towards total edoxaban clearance. A 4-h haemodialysis session caused minimal change in edoxaban exposure.

What is known about this topic?
- Edoxaban is an oral, direct factor Xa inhibitor approved for the prevention of stroke and systemic embolic events in patients with atrial fibrillation with creatinine clearance >95 and for the treatment of acute venous thromboembolic events and prevention of recurrence.
- Approximately 50% of the absorbed dose is cleared by the kidneys.
- Little is known about the effects of haemodialysis in subjects with end-stage renal disease on edoxaban pharmacokinetics, safety, and tolerability.

What does this paper add?
- In this phase 1 trial, haemodialysis accounted for about one-quarter of the clearance of a single 15-mg dose of edoxaban in subjects with end-stage renal disease, and did not significantly remove edoxaban.
- A supplemental dose of edoxaban after haemodialysis may not be needed.
- A single 15-mg dose of edoxaban was well tolerated in subjects with end-stage renal disease.

Small sample size is a limitation to this study. As this was a single-dose study, the impact of haemodialysis on the clearance and total exposure of edoxaban and its active metabolite, M-4, after multiple doses and at steady state cannot be extrapolated from this data. Additionally, the subjects in this study did not have AF or venous thromboembolism. Although no differences are expected in patients who require both anticoagulation and haemodialysis, our results should be interpreted with caution.

In conclusion, a single dose of edoxaban 15 mg in subjects with ESRD receiving haemodialysis was well tolerated and total edoxaban exposure was only slightly decreased by haemodialysis. Based on these single-dose PK data, a supplementary dose of edoxaban may not be required following a haemodialysis session. Importantly, haemodialysis is not an effective mechanism for removal of edoxaban from the blood.

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Conflicts of interest
Dolly A. Parasrampuria, Shuquan Chen, Ling He, Victor Dishy, and Karen S. Brown are employees of Daiichi Sankyo Pharma Development, Edison, NJ. Nobuko Matsushima is an employee of Daiichi Sankyo Co., Ltd., Tokyo, Japan. Prachi K. Wickremasingha was an employee of Daiichi Sankyo Pharma Development at the time this study was conducted. She has no other conflicts of interest to declare. Thomas Marbury is an employee of Orlando Clinical Research Centre. He has no other conflicts of interest to declare.

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