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Original Investigation

Dose-Finding Study of Rivaroxaban in Hemodialysis Patients

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Background: Use of vitamin K antagonists for the prevention of stroke and systemic embolism in dialysis patients with nonvalvular atrial fibrillation is controversial. However, no good alternatives presently are available. The anti−factor Xa antagonist rivaroxaban is contraindicated for lack of pharmacokinetic, pharmacodynamic, and clinical data. This study aims to characterize the pharmacokinetics/pharmacodynamics of rivaroxaban in maintenance hemodialysis patients.

Study Design: Pharmacokinetic and pharmacodynamic study.

Setting & Participants: 18 maintenance hemodialysis patients without residual kidney function at 2 centers.

Drug Administration, Outcomes, & Measurements: (1) A single dose of 10 mg of rivaroxaban was administered at the end of each of 3 consecutive dialysis sessions and area under the curve (AUC) and the effect on coagulation parameters were measured for 44 hours thereafter. (2) A single dose of 10 mg of rivaroxaban was given 6 to 8 hours before a dialysis session and the effect of dialysis on rivaroxaban concentrations was evaluated. (3) To assess potential accumulation, 10 mg of rivaroxaban was given once daily and AUC was measured during 24 hours on days 1 and 7.

Results: Mean $AUC_{0\text{-}44}$ of rivaroxaban plasma concentrations after a single dose of 10 mg was 2,072 μg/L/h, mean maximum concentration was 172.6 μg/L, and mean terminal elimination half-life was 8.6 hours. Dialysis had no appreciable effect on rivaroxaban plasma concentrations. Mean trough concentration after multiple daily doses of 10 mg was 20.2 μg/L.

Limitations: Higher rivaroxaban doses and patients with substantial residual kidney function were not studied.

Conclusions: A 10-mg dose of rivaroxaban in hemodialysis patients without residual kidney function results in drug exposure similar as published for 20 mg in healthy volunteers. Rivaroxaban is not eliminated by dialysis. There is no accumulation after multiple daily dosing. The efficacy and safety of rivaroxaban in hemodialysis patients should be the subject of a large randomized trial.

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INDEX WORDS: Hemodialysis; rivaroxaban; anticoagulant; anti-FXa activity; atrial fibrillation; stroke; end-stage renal disease (ESRD); area under the curve (AUC); pharmacokinetics; pharmacodynamics; dose finding; dose adjustment; dosing guideline.

Atrial fibrillation is common in dialysis patients and its prevalence is increasing.[1] Vitamin K antagonists have been the standard anticoagulant treatment for decades. This is the case even though they require frequent monitoring and bridging with low-molecular-weight heparins because of their unpredictable pharmacology and slow onset and offset of action. Decreased kidney function is associated with a substantial risk of under- and overtreatment.[2] In addition, patients with decreased kidney function receiving warfarin have a higher risk of major bleeding even with good anticoagulation control.[3] Finally, vitamin K antagonists increasingly are implicated in the development of vascular calcifications in this already vulnerable population.[4] A search for alternative anticoagulants therefore is warranted.

Rivaroxaban is a recently developed factor Xa inhibitor with much lower pharmacokinetic variability and little interaction with food and drugs, contributing to consistent, predictable, and dose-proportional anticoagulation.[5-7] Age, sex, and body weight do not influence its action to a clinically relevant degree. As a consequence, routine monitoring is not required. Rivaroxaban has a dual mode of elimination. Approximately two-thirds of the administered dose is metabolized to inactive metabolites in the liver. About half those metabolites are eliminated thereafter by the kidney, and the other half, fecally.[8,9] The remaining third of the dose is renally excreted directly as unchanged active substance in urine, primarily by way of active renal secretion.[8]

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Rivaroxaban has been shown to be effective and safe in large trials on the prevention[10] and treatment of venous thromboembolism,[11] treatment of pulmonary embolism,[12] and prevention of stroke and systemic embolism in nonvalvular atrial fibrillation.[13,14] In ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), 14,264 patients with nonvalvular atrial fibrillation were randomly assigned to receive either dose-adjusted warfarin (target international normalized ratio, 2-3) or rivaroxaban (fixed daily dose of 20 mg for creatinine clearance [CL_{cr}] $\geq$ 50 mL/min or 15 mg for CL_{cr} of 30-49 mL/min).[13] Rivaroxaban was noninferior to warfarin for stroke or systemic embolism prevention, and intracranial and fatal bleeding occurred less frequently.[13] In subgroup analysis of the 2,950 patients with CL_{cr} of 30 to 49 mL/min, the efficacy and safety of rivaroxaban were confirmed.[14] No clinical data in patients with $CL_{cr} < 30$ mL/min are available because this was an exclusion criterion in all clinical trials performed to date.

To our knowledge, at present, only one pharmacokinetic study of rivaroxaban in patients with decreased kidney function has been published.[9] In 24 participants with varying degrees of kidney function, the effect of a single 10-mg dose of rivaroxaban was investigated. In individuals with mildly (CL_{cr}, 66.5 $\pm$ 8.1 mL/min), moderately (CL_{cr}, 42.6 $\pm$ 5.0 mL/min), and severely (CL_{cr}, 22.2 $\pm$ 4.6 mL/min) decreased kidney function, inhibition of factor Xa activity was increased by a factor of 1.5, 1.9, and 2.0, respectively, versus in healthy volunteers.[9]

Based on these limited data, current dosing guidelines for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation advocate a dose reduction from 20 to 15 mg of rivaroxaban in patients with CL_{cr} of 15 to 49 mL/min.[15,16] There are no clinical, pharmacokinetic, or pharmacodynamic studies of rivaroxaban in patients with $CL_{cr} < 15$ mL/min. Its use therefore is not recommended in this population.[15,16]

The objective of the present study was to investigate how the pharmacokinetics and pharmacodynamics of rivaroxaban are affected in patients on maintenance hemodialysis therapy with no appreciable residual kidney function. In addition, the effect of a single dialysis session on the pharmacokinetics and pharmacodynamics of rivaroxaban was studied.

METHODS

Trial Design

The present study was an investigator-driven, 2-center (AZ Sint-Jan Brugge, Belgium, and OLVZ [Onze-Lieve-Vrouwziekenhuis] Aalst, Belgium), nonblinded, cohort study. The study was performed in accordance with the ethical standards of the responsible institutional committee on human experimentation and the Helsinki Declaration of 1975 (and as revised in 1983). The study was registered on www.ClinicalTrials.gov (study number: NCT02047006).

Participants

Patients (men or women aged $\geq$ 18 years) who dialyzed 3 times a week for at least 3 months were eligible. Written informed consent was obtained from each participant. Exclusion criteria were residual kidney function as defined by residual diuresis $>$ 50 mL/d, known intestinal malabsorption or inability to take oral medication, inability to stop comedication that causes major interactions with rivaroxaban (eg, ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort), requirement for therapeutic anticoagulation, contraindication for anticoagulation, and decreased liver function (Child-Pugh classes B and C).

Interventions

1: Rivaroxaban Concentrations and Response Following Single-Dose Administration

Rivaroxaban was given as a single oral dose of 10 mg immediately after each of 3 consecutive dialysis sessions in 12 patients (Fig 1). Patients remained in the hospital from the intake of the first dose until at least 48 hours after the intake of the third dose. Venous blood samples (8.5 mL) were collected using S-Monovette citrate, 3.2% (Sarstedt), immediately before (t = 0) and at t = 0.5, 1, 2, 4, 8, 12, 24, 36, and 44 hours after administration of rivaroxaban. Four aliquots of 1 mL of citrate plasma were stored at −80°C until analysis. Dialysis was performed under standard conditions (blood flow rate = 400 mL/min, dialysis fluid flow rate = 500 mL/min, session duration = 4 hours; and high-flux dialyzer FX60; Fresenius Medical Care) using regional anticoagulation with

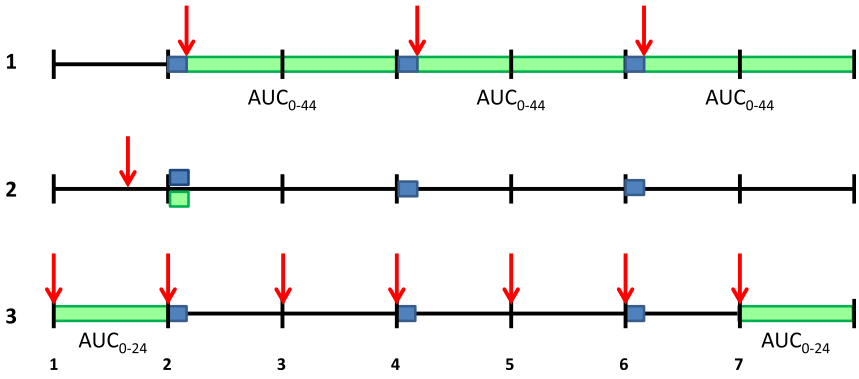

Figure 1. Schematic drawing of study interventions 1 to 3. Blue box, dialysis; green box, sample collection; red arrow, administration of 10 mg of rivaroxaban. Abbreviation: AUC, area under the concentration-time curve.