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Effects of Renal Impairment and Chronic Hemodialysis on the Pharmacokinetics, Pharmacodynamics and Safety of Rivaroxaban

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Abstract

Rivaroxaban is a potent, direct oral Factor Xa inhibitor with high oral bioavailability, predictable pharmacokinetics (PK), and a rapid onset and offset of action. Inhibiting Factor Xa blocks thrombin generation and subsequently thrombin-mediated activation of coagulation. Rivaroxaban has a dual mode of elimination, in which approximately two-thirds of the absorbed dose is hepatically metabolized through oxidative and hydrolytic pathways then excreted as inactive metabolites in both the urine and the feces. The remaining third of the absorbed dose is eliminated as unchanged drug in the urine via P-gp-mediated and ABCG2 (also abbreviated as Bcrp for breast cancer resistance protein)-mediated secretion. Considering the percentage of the administered dose renally eliminated by direct renal excretion as unchanged drug in the urine, the PK and pharmacodynamic (PD) changes that may occur in a renally impaired population were assessed. This assessment consisted of two Clinical Pharmacology studies that were conducted in subjects with various degrees of renal impairment. This review highlights the findings of these two studies.

Keywords: Rivaroxaban; Renal function; Pharmacokinetics; Pharmacodynamics

Introduction

Rivaroxaban is an oral Factor X_a inhibitor. Factor X_a plays a crucial role within the coagulation pathway by catalyzing the conversion of prothrombin to thrombin which amplifies coagulation. Inhibiting this conversion blocks thrombin generation and subsequently thrombin-mediated activation of coagulation. Considering that approximately one-third of the rivaroxaban dose is eliminated by direct renal excretion as unchanged drug in the urine, the pharmacokinetic (PK) and pharmacodynamic (PD) changes that may occur in a renally impaired population were assessed. This assessment consisted of two Clinical Pharmacology studies that were conducted in subjects with various degrees of renal impairment [1,2].

To ensure that these studies met the required level of regulatory rigor, both studies were designed and conducted following the Guidance for Industry: Pharmacokinetics in Patients with impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (Guidance for Industry).

The first of these studies conducted, assessed the PK and PD changes that occur in subjects that have mild, moderate or severe renal impairment [1]. The second study conducted, assessed the PK and PD changes that occur in subjects with end stage renal disease (ESRD) and on dialysis [2]. The following is a brief review of these results:

Study I

Materials and Methods

The aim of this first study was to assess the effects of renal impairment on the PK, PD, and safety and tolerability of single oral dose of rivaroxaban 10 mg.

This study was a non-blinded cohort study of rivaroxaban in subjects with normal renal function and subjects with either mild, moderate, or severe renal impairment. Thirty-two (32) (18 males and 14 females) subjects were divided into four groups based on their level of renal impairment, determined by their creatinine clearance (CL_{Cr}): healthy controls (CL_{Cr} > 80 mL/min), mild impairment (CL_{Cr} 50 – 79 mL/min), moderate impairment (CL_{Cr} 30 – 49 mL/min) or severe impairment (CL_{Cr} <30 mL/min). Serial blood and urine samples for the measurement of rivaroxaban concentrations and non-compartmental PK and PD parameters were collected at selected times throughout the study.

Additionally, to better understand some of the mechanistic changes in the renal clearance (CL_R), both the glomerular filtration and the active secretion fractions were calculated. The PD parameters that were assessed included the inhibition of Factor Xa activity and prolongation of pro-thrombin time in plasma.

Results

Pharmacokinetics

As CL_{Cr} decreased, or renal function worsened in these subjects, the renal clearance (CL_R) of rivaroxaban also decreased. Renal clearance values for healthy controls, mild impairment, moderate impairment, and severe impairment were 2.4 L/h, 1.2 L/h, 0.7 L/h, and 0.5 L/h, respectively. Accordingly, the amount of unchanged rivaroxaban excreted in the urine also decreased from 29% (in healthy controls) to 10% (in subjects with severe impairment). Furthermore, these reduced renal clearances led to an increase in rivaroxaban plasma concentrations demonstrated by changes in the area under concentration-time curve (AUC). Compared with healthy controls, AUC increased by 44%, 52% and 64% in subjects with mild, moderate and severe impairment, respectively. These increases in systemic exposure are a result of reduced renal clearance, not due to an increase in absorption, as the oral bioavailability of a 10-mg dose of rivaroxaban is approximately 100%, meaning close to maximum plasma concentrations are already obtained. Using a previously described [1] population PK model, the mean ratio between active renal secretion and glomerular filtration was approximately 4:1.

Pharmacodynamics

As expected, the administration of rivaroxaban inhibited Factor Xa activity and prolonged the Prothrombin Time (PT). These values increased as renal function declined in a similar manner as the PK. However, it is important to note that the PT prolongation observed in the study was more pronounced in subjects with moderate or severe renal impairment.

Safety and tolerability

Rivaroxaban was well tolerated. No serious adverse events were reported. All non-serious adverse events were classified as either mild or moderate in intensity and none were related to bleeding. The adverse event profile observed was similar to those in other rivaroxaban studies conducted in healthy subjects [1].

Study II

Materials and Methods

The aim of this second study was to analyze the PK, PD and safety profiles of a single 15 mg dose of rivaroxaban administered before and after hemodialysis in patients with end-stage renal disease (ESRD).

This study was an open-label, single-dose, parallel-group study assessing the administration of rivaroxaban in ESRD subjects. Eight healthy subjects, with a $CL_{cr} \geq 80$ mL/min and no evidence of renal disease and 8 subjects with ESRD maintained on hemodialysis for at least 3 months, were enrolled in the study. Healthy control subjects had one treatment period in which they received a single 15 mg dose of rivaroxaban while subjects with ESRD had 2 treatment periods. The first period consisted of a single 15 mg dose 2 +/- 0.5 hour before the start of a 4-hour hemodialysis session followed by a 7- to 14-day washout period. The second period consisted of a single 15 mg dose 3 hour after the completion of the hemodialysis session. All doses were administered with meals.

Results

Pharmacokinetics

Subjects with ESRD dosed 3 hours after the hemodialysis session experienced a 35% decrease in overall rivaroxaban clearance, which is consistent with the estimated overall clearance of 36% reported in previous trials and the drug package insert [3,4]. This reduction in overall clearance led to a 56% increase in overall systemic exposure (AUC). Compared to this 56% post-dialysis increase, when dosed prior to their hemodialysis session, subjects experienced only a 5% lowering of AUC. This slight 5% difference in AUC values between pre-dialysis and post-dialysis dosing indicates that dialysis has very little impact on the pharmacokinetics of rivaroxaban. The mean ratio of active transport to passive filtration was approximately 3:1 in the ESRD subjects, a trend that is consistent to that observed in the first study.

Pharmacodynamics

Once again, the administration of rivaroxaban inhibited Factor Xa activity and prolonged the PT. Changes in PT and Factor Xa inhibition was higher in patients with ESRD, when compared to the healthy subjects. The degree that these two outcomes changed was generally associated with the changes seen in plasma pharmacokinetics.

Safety and tolerability

None of the adverse events reported were deemed serious and none were related to bleeding. The adverse events that occurred were consistent with those previously reported in other clinical pharmacology studies.

Discussion

Study results showed that with a decrease in renal function, rivaroxaban exposure (AUC) increased (PK), which also led to an increase in Factor Xa inhibition and PT prolongation (PD). However, there appears to be a plateau in this increased exposure between moderate and severe renal impairment. This is apparent when assessing the ESRD data along with the other renal impairment data, which shows a comparable systemic exposure increase as what was observed with those with moderate and severe renal impairment. The rationale for this plateau effect is likely based on the availability of renal P-gp transporters (the active transport function for clearing the parent drug); a gradual loss of these transporters with decreasing renal function may reach a maximum around moderate to severe renal impairment and before there is a

complete loss of passive filtration. This maximum loss of renal P-gp transporters would be significant for a drug like rivaroxaban, which depends more on active transport than passive filtration (approximately 3:1) for drug removal **(Table 1).**

Table 1: Rivaroxaban exposure (AUC) geometric mean ratio (Renally impaired vs. Healthy controls) [1,2].

Level of Renal Impairment	AUC Increase
Mild (CL_{Cr} > 80 mL/min) [1]	44%
Moderate (CL_{Cr} 50 – 79 mL/min) [1]	52%
Severe (CL_{Cr} < 30 mL/min) [1]	64%
ESRD (CL_{Cr} < 15 mL/min) [2]	56%

While patients with severe renal impairment or ESRD were not studied in the Phase 3 safety and efficacy trials, due to the similar exposure changes between those with moderate and severe renal impairment observed in the first study [1], the label allows for those with severe renal impairment and non-valvular atrial fibrillation to receive the same 15 mg dose: "For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of XARELTO is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal." Additionally, due to the similar exposure changes between those with moderate renal impairment and ESRD as described in the second study [2], and the fact that these are similar to the exposures observed in the ROCKET-AF study with moderate renal impairment, a 15 mg dose may be considered: "In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF."

Conclusion

Patients with renal impairment being treated for non-valvular atrial fibrillation are at increased risk for thromboembolism and bleeding events. Our findings are consistent with the findings of other studies conducted in this space proving that rivaroxaban provides a safe and effective alternative to warfarin in patients with renal dysfunction. According to a review of ROCKET AF conducted by Fox et al comparing rivaroxaban with warfarin in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, patients with moderate renal dysfunction receiving a 15mg dose of rivaroxaban preserved the treatment effect of warfarin without increasing bleeding and had fewer fatal bleeds [5]. Similarly, additional insights from ROCKET AF that assessed treatment outcomes in patients treated with rivaroxaban or warfarin showed that in patients with worsening renal function, rivaroxaban was associated with no increase in the composite bleeding end point when compared with warfarin [6].

Clinically, patients that experience a decline in renal function during the course of anticoagulation treatment can be maintained on the same rivaroxaban dose while being less likely to experience undesirable increases in drug exposure. However, it is important to note that there are no clinical (safety or efficacy) data available regarding the use of rivaroxaban in patients with severe renal impairment (CL_{Cr} < 30 mL/min) or in patients with ESRD undergoing dialysis.

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