

Pharmacokinetics (PK) and Pharmacodynamics (PD) of Rivaroxaban: A Comparison of Once- and Twice-daily Dosing in Patients Undergoing Total Hip Replacement (THR)

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Presented at ISTH. 2007.

INTRODUCTION

Rivaroxaban is an oral, direct Factor Xa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. Two double-blind, phase IIb, dose-finding studies with rivaroxaban for the prevention of venous thromboembolism (VTE) after total hip replacement (THR) were conducted: one with rivaroxaban given twice daily (bid; total

daily doses of 5–60 mg),¹ and one with rivaroxaban given once daily (od; range 5–40 mg).² In the bid study, rivaroxaban total daily doses of 5–20 mg had similar efficacy and safety to enoxaparin. In the od study, 10 mg od—a dose within the range identified by the bid studies—had the optimal combination of efficacy and safety for further investigation.

OBJECTIVES

A population analysis to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban given once or twice daily for VTE prevention in patients undergoing THR.^{1,2}

METHODS

- Blood samples were taken from all patients using a sparse sampling approach. Profile days were early after surgery and at rivaroxaban steady state
- Rivaroxaban plasma concentrations and prothrombin time (PT) were determined at a central laboratory
 - For determination of PT, freeze-dried thromboplastin from rabbit brain, with an international sensitivity index (ISI) of 1.8 was used in the bid study (STA Neoplastine®); recombinant human thromboplastin with an ISI of 1.0 was used in the od study (Innovin®)
- Population PK and PK/PD analyses were performed using non-linear, mixed-effect modeling, allowing analysis of the influence of pre-specified demographic factors

- Due to the favourable efficacy and safety of the lower rivaroxaban doses,^{1,2} the PK model was calculated using only the 5, 10 and 20 mg total daily dose groups. Data from the same total daily dose groups were pooled. The final model was used to predict rivaroxaban maximum and minimum plasma concentration (C_{max} and C_{trough} , respectively), and area under the plasma concentration–time curve (AUC) values
- PK/PD analyses, including all dose groups, were performed to determine how rivaroxaban plasma concentrations correlated with PT in each study

CONCLUSION

- The final pooled PK model described the PK of rivaroxaban well, whether it was given od or bid, demonstrating that the PK of rivaroxaban were predictable
- Rivaroxaban is predominantly excreted renally (66%),³ so the effect of renal function and age (which influences renal function) on the clearance of rivaroxaban was expected
- The moderate influence of demographic factors on the PK of rivaroxaban, and the simulation, suggested that fixed dosing of rivaroxaban 10 mg od should be feasible in all patients
- Rivaroxaban C_{max} was higher, and C_{trough} was lower, in the od study compared with the bid study, when the same total daily

doses were compared; however, the 90% CIs overlapped

- There was a similar low risk of bleeding and VTE with both od and bid dosing of rivaroxaban in these studies^{1,2}

- PT correlated closely with rivaroxaban plasma concentrations
- In conclusion, the PK and PD of rivaroxaban were predictable and consistent, whether it was administered od or bid, in patients receiving it for VTE prevention after THR, supporting the selection of a fixed rivaroxaban 10 mg od dose for phase III studies

RESULTS

- A total of 758 patients provided samples for the PK analysis (bid study: 362 patients; od study: 396 patients). PT measurements for the PK/PD analyses were available from 516 and 665 patients from the bid and od studies, respectively
- Patients' demographics were similar between the two patient populations

Pharmacokinetics of rivaroxaban

- The PK of rivaroxaban were well described by an oral, one-compartment model with a first-order absorption rate constant
- In both studies, absorption and clearance of rivaroxaban were more variable early after surgery than at steady state. This is expected for an oral drug in patients who have undergone major surgery

Influence of demographic factors on the pharmacokinetics of rivaroxaban

The influence of demographic factors on the PK of rivaroxaban was moderate and within the variability of the patient population.

- Clearance of rivaroxaban was affected by study day, age, renal function, serum albumin and haematocrit (Table 1)
- The volume of distribution of rivaroxaban was affected by body weight (Table 1)
- Simulations of rivaroxaban plasma concentrations in patients with 'extreme' demographics receiving 10 mg od suggested that this fixed dose would be suitable for all of these patients (Figure 1)

Pharmacokinetic parameters of rivaroxaban

- Rivaroxaban PK increased dose dependently in both studies (Table 2)
- As would be expected, the C_{max} of rivaroxaban was higher, and C_{trough} was lower, in the od study compared with the bid study, when the same total daily doses were compared; however, the 90% confidence intervals (CIs) overlapped (Table 2)

Rivaroxaban plasma concentration/prothrombin time correlation

- In both studies, PT correlated with rivaroxaban plasma concentrations following a simple, linear intercept model (Figure 2)
 - The different slopes of the PK/PT correlations in the bid and od studies were probably due to the use of different thromboplastin reagents. This finding is the subject of ongoing investigations

Table 1. Influence of demographic factors on the pharmacokinetics (PK) of rivaroxaban in patients undergoing total hip replacement, receiving total daily rivaroxaban dose of 5–20 mg (N=758)

Study day	Affected PK parameter	Effect	
		CL	Effect
Study day	CL	Mean CL of 5.46 l/h on the first post-operative day, increasing to 7.51 l/h at steady state	
Age	CL	Decrease of 1.0% per year older than the median of 66 years (and vice versa)	
Renal function	CL	Decrease of 0.3% per 1 ml/min less than the median calculated creatinine clearance of 88.1 ml/min (and vice versa)	
Serum albumin	CL	Increase of 2.2% per 0.1 g/dl more than the median of 4 g/dl (and vice versa)	
Haematocrit	CL	Increase of 1.2% per 1% haematocrit more than the median of 37.3% (and vice versa)	
Body weight*	V	Decrease of 6.4% per 0.1 m ² below the median body surface area of 1.84 m ² (and vice versa)	

CL, clearance; V, volume of distribution
 *Body weight was expressed as body surface area in the final model

Table 2. Median predicted rivaroxaban pharmacokinetic parameters in total hip replacement patients at steady state (with 90% confidence intervals)

Parameter	Rivaroxaban total daily dose		
	5 mg	10 mg	20 mg
n (bid/od)	122/124	122/140	118/132
C_{max} µg/l			
bid	39.7 (29.2–73.4)	65.2 (46.2–105)	141 (101–218)
od	69.0 (49–112)	124 (88.1–194)	222 (160–360)
C_{trough} µg/l			
bid	8.61 (1.71–26.5)	15.4 (4.65–46.2)	34.9 (7.85–99.7)
od	4.50 (0.7–37.7)	9.12 (1.34–37.8)	22.4 (4.3–95.7)
AUC _{0–24} µg·h/l			
bid	531 (204–1188)	915 (583–1637)	1982 (1139–3757)
od	670 (377–1283)	1170 (767–2077)	2374 (1366–4858)

bid, twice daily; od, once daily

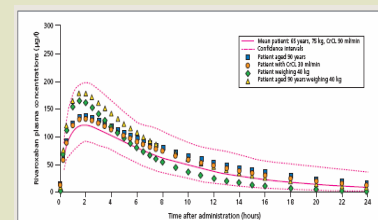


Figure 1. 'Extreme' case simulations of rivaroxaban plasma concentrations in patients with extreme age, severe renal impairment, low body weight, or extreme age and low body weight receiving rivaroxaban 10 mg once daily. CL_{CR}, creatinine clearance.

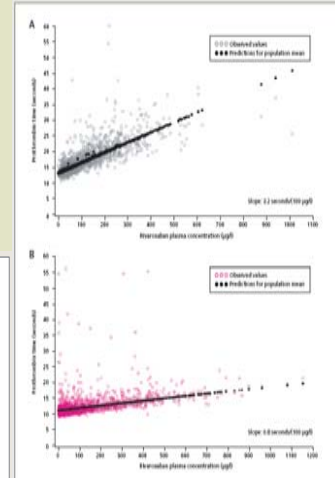


Figure 2. Correlation between prothrombin time and rivaroxaban plasma concentration at steady state in (A) the twice-daily study and (B) the once-daily study.

References

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