The effect of age, gender and weight on the safety and pharmacology of rivaroxaban (BAY 59-7939) – a novel, oral, direct Factor Xa inhibitor

Dagmar Kubitza[1], Michael Becka[2], Wolfgang Mueck[1], Michael Zuehlsdorf[1]
[1]Clinical Pharmacology, and [2]Department of Biometry, Pharmacometry, Bayer HealthCare AG, Wuppertal, Germany

Introduction

- Currently available anticoagulants – which are recommended for a variety of conditions, including the prevention of venous thromboembolism (VTE) after major orthopaedic surgery – often require dose adjustment in older patients, patients with extreme body weight, and for gender
- Rivaroxaban (BAY 59-7939) is a novel, oral, direct Factor Xa (FXa) inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders, including thromboprophylaxis after major orthopaedic surgery

Objectives

- In order to determine whether fixed dosing of rivaroxaban may be feasible in the clinical setting, the influences of age, gender and weight on the pharmacology and safety of rivaroxaban in healthy subjects were investigated

Subjects and Methods

Study designs and treatments

- Two randomized, single-blind, placebo-controlled, parallel-group studies were conducted in Caucasian subjects
  - One study investigated the effects of age and gender on the pharmacology and safety of rivaroxaban in subjects enrolled in four discrete groups: young males or females (aged 18–45 years), and elderly males or females (aged >75 years)
  - The second study investigated the effects of weight on the pharmacology and safety of rivaroxaban in subjects in three weight groups (≤50 kg, 70–80 kg [normal] and >120 kg)
- Subjects were randomly assigned to receive a single dose of rivaroxaban 10 mg or placebo
- Both studies were conducted in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. Subjects provided written, informed consent

Assessments

- The pharmacokinetic (PK) parameters assessed included rivaroxaban exposure (measured by the area under the concentration–time curve) and maximum rivaroxaban plasma concentrations (C_{max})
- The pharmacodynamic (PD) effects of rivaroxaban were measured by assessing inhibition of FXa activity and prolongation of prothrombin time (PT)
- An exploratory ANOVA was used to investigate the effects of age, gender and weight on the PK and PD parameters
- Subjective and objective safety and tolerability were assessed

Results

Study populations

- A total of 34 healthy subjects were enrolled in the age and gender study (Table 1)
  - A young female withdrew from the study after dosing; therefore, 33 subjects were valid for PK and PD analyses and 34 for safety analysis
- A total of 48 subjects were enrolled in the weight study (Table 2)
  - The ≤50 kg group contained females only, because it was not possible to find healthy, adult, Caucasian, male subjects of this weight

Table 1. Demographics of the age and gender study population (n=34)

Parameter	Young males (n=9*)	Young females (n=9*)	Elderly males (n=8*)	Elderly females (n=8*)
Age[a] (years)	30.3 (18.0–43.0)	33.9 (22.0–43.0)	76.8 (74.0–83.0)	77.8 (75.0–83.0)
Weight[b] (kg)	81.3±13.7	70.0±6.9	80.1±11.4	67.4±7.2
Height[b] (cm)	181.4±8.9	168.7±6.6	171.4±7.2	159.4±4.3
Body mass index[b] (kg/m^2)	24.6±3.3	24.6±2.5	27.2±1.8	26.6±3.0
Creatinine clearance[b] (ml/min)	120.0±9.3	121.0±20.1	59.1±6.0	51.8±18.4

[a]Mean (range); [b]mean ± standard deviation; *six subjects received rivaroxaban, the remainder received placebo

Table 2. Demographics of the weight study population (n=48)

Parameter	Placebo all weights (n=12)	Rivaroxaban 10 mg ≤50 kg (n=12)	Rivaroxaban 10 mg 70–80 kg (normal; n=12)	Rivaroxaban 10 mg >120 kg (n=12)
Age[a] (years)	34.3 (20–50)	35.3 (22–46)	32.3 (20–54)	37.1 (22–47)
Gender (male/female)	4/8	0/12	6/6	6/6
Weight[b] (kg)	81.7±34.4	48.3±0.9	74.0±2.2	132.2±9.9
Height[b] (cm)	167.5±11.1	158.4±4.7	175.1±8.9	174.7±7.9
Body mass index[b] (kg/m^2)	28.5±10.4	19.3±1.1	24.3±2.3	43.5±4.2

[a]Mean (range); [b]mean ± standard deviation

Pharmacokinetics and pharmacodynamics

Age

- The C_{max} of rivaroxaban was not affected by age; however, rivaroxaban exposure was 41% higher in elderly compared with young subjects (Figure 1A)
  - This age-related effect could be explained partially by delayed renal clearance of rivaroxaban in elderly subjects
- Rivaroxaban inhibited FXa activity and prolonged PT, whereas placebo had no effect; the maximum effect of rivaroxaban on these parameters occurred 2–4 hours after administration of rivaroxaban (Figure 2A and B)
- Compared with young subjects, elderly subjects had an increased area under the effect–time curve (AUEC) for inhibition of FXa activity and prolongation of PT (58% and 46%, respectively), because rivaroxaban plasma concentrations took longer to return to baseline in elderly subjects (Figure 2A and B)

Gender

- Gender did not have any significant effect on the C_{max} of rivaroxaban, or on rivaroxaban exposure (Figure 1A)
- Inhibition of FXa activity and prolongation of PT were not significantly affected by gender (Figure 2A and B)

Weight

- Rivaroxaban exposure was not influenced by weight, and there was no relevant difference in the C_{max} of rivaroxaban between the >120 kg group and the normal weight group; however, C_{max} increased by approximately 24% in the ≤50 kg weight group compared with normal-weight subjects (Figure 1B)
- The maximum effect of rivaroxaban on inhibition of FXa activity and prolongation of PT occurred 2–4 hours after administration of rivaroxaban (Figure 3A and B)
- The increase in C_{max} in subjects weighing ≤50 kg had no substantial effect on inhibition of FXa activity or prolongation of PT

Safety and tolerability

- Rivaroxaban was well tolerated by all subjects across both studies; all events were mild to moderate in intensity and resolved without treatment

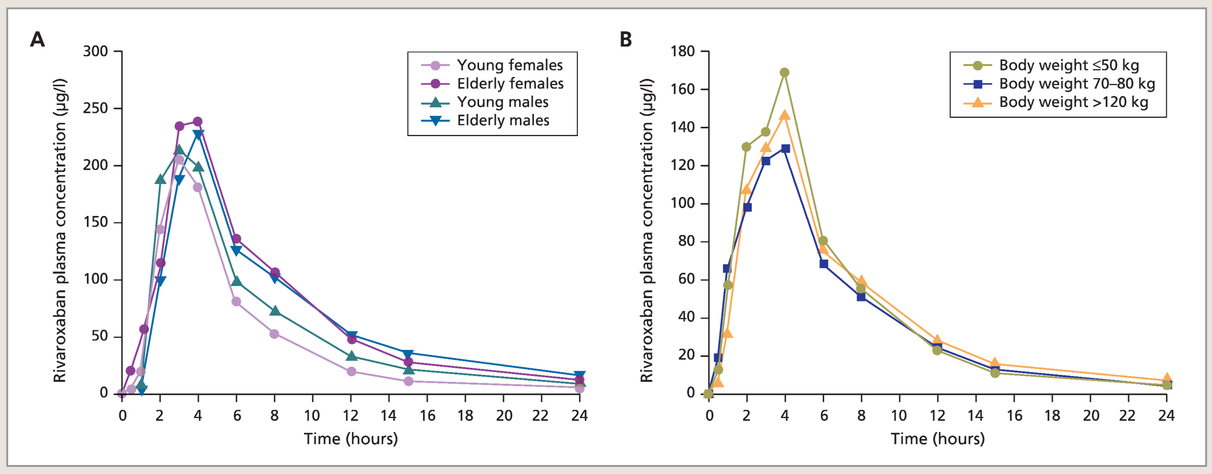

Figure 1. Mean plasma concentrations of rivaroxaban after administration of 10 mg to (A) healthy young (18–45 years) and elderly (>75 years) male and female subjects, and (B) healthy male and female subjects in three weight groups

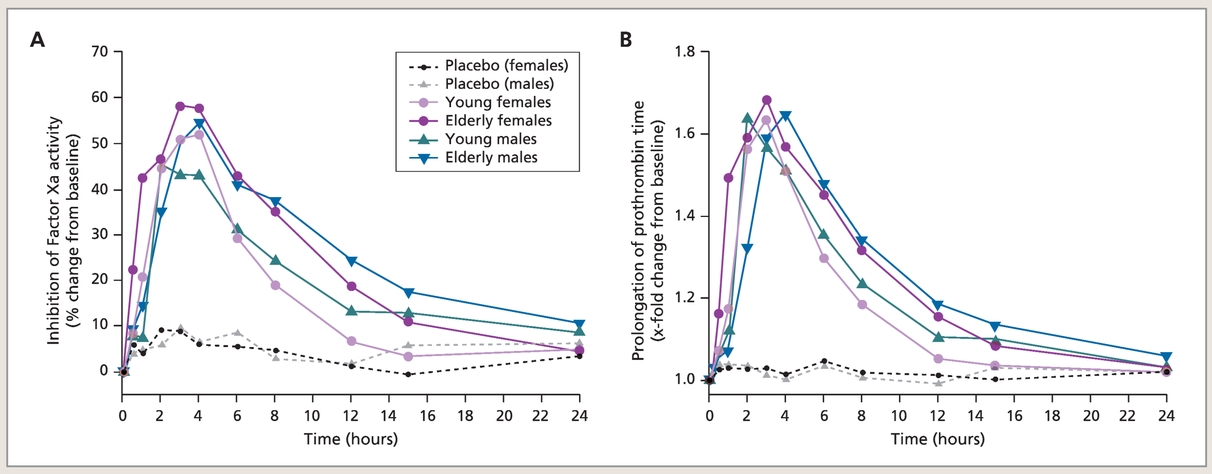

Figure 2. (A) Median inhibition of Factor Xa activity and (B) median prolongation of prothrombin time after a single dose of rivaroxaban 10 mg or placebo in healthy young (18–45 years) and elderly (>75 years) male and female subjects

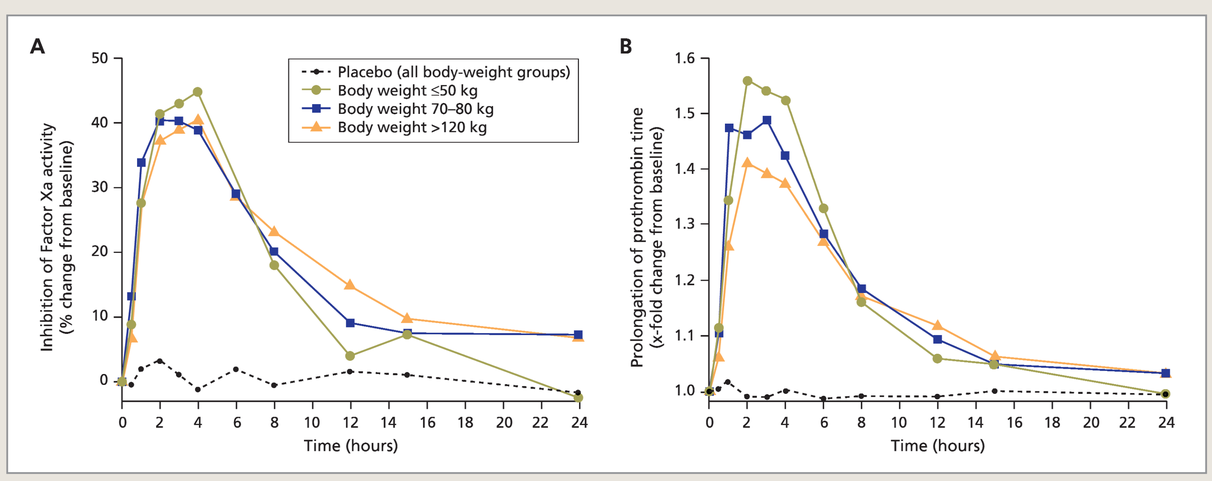

Figure 3. (A) Median inhibition of Factor Xa activity and (B) median prolongation of prothrombin time after administration of rivaroxaban 10 mg or placebo to healthy, male and female subjects in three weight groups

Conclusions

- Rivaroxaban exposure and the AUEC for PD effects were slightly higher in elderly compared with young subjects. This was thought to be partially due to delayed renal clearance of rivaroxaban caused by decreased renal function, a well-accepted consequence of advancing age[1]
- Gender had no significant effect on the PK or PD of rivaroxaban
- Weight had only a small influence on the PK and PD of rivaroxaban; the small increase in the C_{max} of rivaroxaban observed in subjects with low body weight (~24%) was not thought to be clinically relevant
- Rivaroxaban was well tolerated in all subjects, regardless of age, gender or weight
- Overall, these results suggest that rivaroxaban may be administered at a fixed dose, irrespective of age, gender or weight
  - Phase II studies of rivaroxaban for the prevention of VTE after major orthopaedic surgery support this conclusion; in these studies, fixed doses of rivaroxaban were administered to male and female patients aged 26–93 years, weighing between 45 and 173 kg[2–4]
  - Confirmation of these findings may be provided by the ongoing phase III programme in this indication, in which rivaroxaban will be administered in fixed doses irrespective of age, gender or body weight

References

1. Clark B. *Adv Ren Replace Ther* 2000;7:11–21
2. Eriksson BI *et al. J Thromb Haemost* 2006;4:121–128
3. Eriksson BI *et al. Circulation* 2006;114:2374–2381
4. Turpie AG *et al. J Thromb Haemost* 2005;3:2479–2486

scios

Bayer HealthCare