Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Before this study was started, it was already known that approximately two-thirds of the administered rivaroxaban dose is metabolized by the liver to inactive metabolites.
- It was anticipated that hepatic impairment would influence the pharmacokinetics and pharmacodynamics of rivaroxaban.

WHAT THIS STUDY ADDS

- The results of this study provide detailed information on the influence of mild and moderate hepatic impairment on the pharmacokinetics and pharmacodynamics of rivaroxaban.
- The data showed that moderate (but not mild) hepatic impairment reduced total body clearance of rivaroxaban after a single 10 mg dose, leading to increased rivaroxaban exposure and pharmacodynamic effects.

AIM

This study investigated the effects of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban (10 mg), an oral, direct Factor Xa inhibitor.

METHOD

This single centre, non-randomized, non-blinded study included subjects with mild ($n = 8$) or moderate hepatic impairment ($n = 8$), according to the Child–Pugh classification, and gender-matched healthy subjects ($n = 16$).

RESULTS

Rivaroxaban was well tolerated irrespective of hepatic function. Mild hepatic impairment did not significantly affect the pharmacokinetics or pharmacodynamics of rivaroxaban, compared with healthy subjects. However, in subjects with moderate hepatic impairment, total body clearance was decreased, leading to a significant increase in the area under the plasma concentration–time curve (AUC). The least-squares (LS)-mean values for AUC were 1.15-fold [90% confidence interval (CI) 0.85, 1.57] and 2.27-fold (90% CI 1.68, 3.07) higher in subjects with mild and moderate hepatic impairment, respectively, than in healthy subjects. Consequently, the pharmacodynamic responses were significantly enhanced in subjects with moderate hepatic impairment. For inhibition of Factor Xa, increases in the area under the effect–time curve and the maximum effect were observed, with LS-mean ratios of 2.59 and 1.24, respectively, vs. healthy subjects. Prolongation of prothrombin time was similar in healthy subjects and those with mild hepatic impairment, but was significantly enhanced in those with moderate hepatic impairment.

CONCLUSION

Moderate (but not mild) hepatic impairment reduced total body clearance of rivaroxaban after a single 10 mg dose, leading to increased rivaroxaban exposure and pharmacodynamic effects.

Introduction

Anticoagulants are recommended for the prevention and treatment of arterial and venous thromboembolic disorders [1–5]. Traditional anticoagulants, such as vitamin K antagonists, unfractionated heparin, low molecular weight heparins and the indirect Factor Xa inhibitor fondaparinux, are effective but have limitations [6–8]. Unfractionated heparin, low molecular weight heparins and fondaparinux must be given parenterally, which is an inconvenient route of administration for long term and out of hospital use. Vitamin K antagonists (such as warfarin) have a narrow therapeutic window, variable pharmacokinetics and pharmacodynamics, and extensive food and drug interactions, which necessitate regular coagulation monitoring and dose adjustment [7]. Newer oral anticoagulants have been developed in recent years to address some of these shortcomings. These novel agents (e.g. rivaroxaban, apixaban and dabigatran etexilate) specifically and directly target Factor Xa or thrombin, which are key factors in coagulation activation and clot formation.

Rivaroxaban, an oral, direct Factor Xa inhibitor, has demonstrated dose-dependent anticoagulant effects over a wide dose range and has been found to have predictable pharmacokinetics and pharmacodynamics in phase I and phase II studies [9–12]. Rivaroxaban has been investigated in a number of large scale, randomized phase III studies across several indications for the prevention and treatment of thromboembolic disorders. Based on the outcomes of the phase III RECORD studies [13–16], the rivaroxaban 10 mg dose was approved for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. In light of the positive outcomes of the phase III EINSTEIN DVT, EINSTEIN EXT and ROCKET AF studies [17, 18], rivaroxaban has also been approved by the European Medicines Agency (EMA) for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism after an acute DVT, and by the EMA and the US Food and Drug Administration for stroke prevention in patients with non-valvular atrial fibrillation. In addition, a phase III study investigating rivaroxaban, in addition to antiplatelet therapy, for the secondary prevention of coronary events in patients with an acute coronary syndrome (ATLAS ACS 2 TIMI 51) met its primary efficacy endpoint, with significant reductions in the composite endpoint of cardiovascular death, myocardial infarction or stroke [19].

The liver plays an important role in the process of blood coagulation, because it synthesizes the majority of the clotting factors and inhibitors of the coagulation pathway [20]. Subjects with hepatic impairment have decreased synthesis of coagulation factors and, therefore, may be at increased risk of bleeding as a result of impaired haemostasis [20, 21]. Overall severity of hepatic impairment is usually graded according to the Child–Pugh classification (grade A mild hepatic impairment, grade B moderate

hepatic impairment and grade C severe hepatic impairment) [22, 23]. It has been demonstrated that the reduction in the levels of clotting factors correlates well with the severity of hepatic impairment (expressed as the Child–Pugh score) [21]. Hepatic impairment can also affect the pharmacokinetics of drugs that are metabolized by the liver, which may result in increased drug exposure and the need for dose adjustment in patients with hepatic impairment [24].

Rivaroxaban has a dual mode of elimination. Of the administered dose, one-third undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion [25, 26]. *In vitro* investigations have shown that rivaroxaban is a substrate of the transporter proteins P-glycoprotein (P-gp) and breast cancer resistance protein [27]. The remaining two-thirds of the administered dose is metabolized by the liver to inactive metabolites via the cytochrome P450 (CYP) enzymes CYP3A4 and CYP2J2 and by CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are sites of biotransformation. There are no major or active circulating metabolites, and elimination occurs via both renal and faecal routes [25, 26].

Because the liver provides an important route of elimination of rivaroxaban, and liver insufficiency affects blood coagulation status, the objectives of the current study were to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of rivaroxaban after the administration of a single oral 10 mg dose to subjects with mild or moderate hepatic impairment due to cirrhosis, stratified according to the Child–Pugh classification (grade A or B, respectively) and in age-, weight- and gender-matched healthy control subjects.

Methods

Subjects

Men and women with stable liver disease resulting from liver cirrhosis (confirmed by histology, laparoscopy or ultrasound), which led to mild or moderate hepatic impairment according to the Child–Pugh classification [22, 23], were eligible for the study. Bilirubin, serum albumin, prothrombin time (PT), hepatic encephalopathy and ascites levels were measured and categorized on a scale of 1–3 (mild to severe degradation) for each assessment, to a maximum of 15 points. Mild and moderate hepatic impairments were assessed as grade A (total score of 5–6) and grade B (total score of 7–9), respectively. For each eligible patient, an age- (± 10 years), weight- (± 10 kg) and gender-matched healthy subject was enrolled. To be enrolled into the study, subjects had to be aged 18–65 years (hepatic impairment, $n = 16$) or 18–70 years (healthy subjects, $n = 16$), with a body mass index of 18–34 kg m⁻².

Subjects were excluded from the study if they met any of the following criteria: known coagulation disorders, increased bleeding risk, sensitivity to common causes of bleeding (e.g. nasal bleeding), history of gastrointestinal disease that could interfere with absorption of rivaroxaban or concomitant use of drugs that influence the coagulation system or interfere with hepatic metabolism. In addition, exclusion criteria for subjects with hepatic impairment included: significant cardiovascular, endocrine, haematological, psychiatric or other chronic disease, the use of strong CYP3A4 inducers or inhibitors in the 30 days prior to dosing, primary or secondary biliary cirrhosis or sclerosing cholangitis, renal impairment (creatinine clearance ≤ 40 ml min⁻¹), grade III/IV hepatic encephalopathy or severe ascites (>6 l). Women who were pregnant, lactating or not using adequate contraception were ineligible, as were subjects who had participated in another clinical trial within the preceding 2 months. Written, informed consent was obtained from subjects who participated in the study.

Study design and treatment

This single centre, non-randomized, non-blinded, parallel group, non-controlled study was approved by the Ethics Committee of Schleswig-Holstein, Bad Segeberg, Germany, and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice and German drug law.

Subjects were assessed for suitability at a screening visit within 2 weeks prior to dosing. On the morning of the treatment day (day 0), a single 10 mg rivaroxaban oral dose (as two 5 mg tablets) was administered after a fasting period of ≥ 10 h. Subjects stayed at the clinic on the treatment day and on the follow-up days (days 1 and 2). After discharge, subjects returned to the clinic on the morning of day 3 and for a final examination approximately 5–14 days after rivaroxaban administration.

Assessments

Pharmacokinetic parameters Serial venous blood samples (4 ml) to determine rivaroxaban plasma concentrations were collected before dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after rivaroxaban administration. Additional blood samples (6 ml) were collected 2, 4 and 8 h after rivaroxaban administration to determine the fraction of unbound rivaroxaban in the plasma (f_u) and serum albumin. Urine was collected over a 48 h period after rivaroxaban administration on day 0, with collection intervals of 0–4, 4–8, 8–12, 12–24 and 24–48 h. All samples were stored at -15°C or below until analysis.

Plasma and urine concentrations of unchanged rivaroxaban were analyzed after solid phase extraction by high pressure liquid chromatography (system HP 1100, Hewlett-Packard, Waldbronn, Germany) coupled with tandem mass spectrometry (API 3000, Applied Biosystems, Darmstadt, Germany). A close chemical analogue of rivaroxaban was used as an internal standard [28]. In plasma, the analytical

range was 0.5–500 $\mu\text{g l}^{-1}$, and plasma concentrations of rivaroxaban were determined with an accuracy of 97.6–102.0% and a precision of 3.8–5.4%. In urine samples, the analytical range was 0.997–19.9 mg l⁻¹, and urine concentrations of rivaroxaban were determined with an accuracy of 94.0–105.0% and a precision of 4.7–9.4%.

Plasma protein bound and free (unbound) rivaroxaban were separated by equilibrium dialysis, where the free rivaroxaban diffused through a semipermeable membrane into the buffer until it reached equilibrium. After dialysis, rivaroxaban concentrations in buffer samples were analyzed using liquid chromatography-mass spectrometry and used to calculate the f_u of rivaroxaban in plasma. The calibration range was 0.5–500 $\mu\text{g l}^{-1}$, and the concentrations of control samples were determined with an accuracy of 96.0–100.0% and a precision of 2.0–7.2%.

Pharmacokinetic parameters were calculated using non-compartmental methods. The primary pharmacokinetic parameters analyzed included area under the plasma concentration–time curve (AUC), AUC_u (based on unbound plasma concentrations), maximum concentration in plasma (C_{max}), $C_{\text{max,u}}$, half-life associated with terminal slope ($t_{1/2}$) and f_u . The secondary pharmacokinetic parameters included AUC and C_{max} normalized to dose per kg of body weight (AUC_{norm}, $C_{\text{max, norm}}$, respectively), time to reach peak plasma concentrations (t_{max}), amount of rivaroxaban excreted in the urine (Ae_{ur}), total body clearance of rivaroxaban from plasma (CL/F) and renal clearance of rivaroxaban (CL_R).

Pharmacodynamic parameters Blood samples (8 ml) were collected immediately before (0) and 1, 2, 3, 4, 6, 8, 12, 15, 24, 48 and 72 h after rivaroxaban administration for pharmacodynamic assessments. The following pharmacodynamic parameters were assessed: inhibition of Factor Xa activity, ecarin-stimulated thrombin activity, antithrombin activity (Chromogenix, Milan, Italy; method based on supplier's instructions), PT, activated partial thromboplastin time (Roche Diagnostics, Mannheim, Germany) and HepTest (American Diagnostica, Stamford, CT, USA). All assays were performed according to the manufacturers' instructions. Parameters calculated for the inhibition of Factor Xa activity and PT prolongation included maximum effect (E_{max}), time of maximum effect (t_{max}), time of last observation used in calculations [time of last observation (t_n) up to 48 h], and area under the effect–time curve between rivaroxaban administration (0) and t_n (AUC(0, t_n)).

Safety and tolerability Safety and tolerability were assessed for up to 72 h after administration of rivaroxaban and at the final examination. Subjective tolerability was evaluated by questioning subjects about any adverse events and by subjects' spontaneous reporting of adverse events. Adverse events were classified according to severity (mild, moderate or severe) and importance (serious or non-serious). Objective tolerability was measured by

Table 1Summary of characteristics of all subjects included in the study ($n = 32$) and by degree of hepatic impairment

	Healthy subjects ($n = 16$)	Mild hepatic impairment* ($n = 8$)	Moderate hepatic impairment† ($n = 8$)	All subjects ($n = 32$)
Male/female (n)	9/7	5/3	4/4	18/14
Age (years)	54.3 ± 9.4	58.4 ± 6.8	51.9 ± 10.1	54.7 ± 9.0
Weight (kg)	76.0 ± 11.4	81.1 ± 15.7	73.3 ± 13.3	76.6 ± 12.9
Height (cm)	171.4 ± 7.4	174.4 ± 10.8	169.4 ± 9.3	171.7 ± 8.7
Body mass index (kg m^{-2})	25.8 ± 2.8	26.6 ± 3.7	25.5 ± 4.2	25.9 ± 3.3
Creatinine clearance (ml min^{-1})	134.5 ± 52.3 (81.1–287.2)	101.3 ± 24.2 (73.1–130.9)	130.8 ± 82.6 (44.9–311.1)	125.2 ± 56.5 (44.9–311.1)
Range				
Serum albumin (g dl^{-1})				
Male	4.4 ± 0.2	4.4 ± 0.4	3.4 ± 0.4	–
Female	4.3 ± 0.3	4.6 ± 0.2	3.8 ± 0.7	–
Prothrombin time (s)				
Male	12.0 ± 1.0	12.5 ± 1.0	16.1 ± 1.6	–
Female	12.7 ± 1.0	12.4 ± 0.6	15.3 ± 1.2	–
Total bilirubin (mg dl^{-1})				
Male	0.7 ± 0.4	0.6 ± 0.2	1.9 ± 1.0	–
Female	0.5 ± 0.2	0.4 ± 0.2	2.4 ± 1.3	–

Data are given as mean $\pm$ SD unless indicated otherwise. *Child–Pugh grade A. †Child–Pugh grade B.

monitoring haematological parameters, clinical chemistry, cardiovascular parameters (heart rate and blood pressure in supine position after a resting period of 15 min) and ECG parameters (recorded after a resting period of 15 min).

Statistical analyses

The pharmacokinetic characteristics AUC , AUC_{0-t} , $C_{\max}$ and $C_{\max,u}$ of rivaroxaban and the derived pharmacodynamic parameters $E_{\max}$ and $AUC(0,t_n)$ for inhibition of Factor Xa activity and prolongation of PT were analyzed assuming log-normally distributed data. To compare parameters between the strata, the logarithms of these characteristics were analyzed using analysis of variance (ANOVA) including a group and a gender effect as well as their interaction. Applying log-transformation to the parameters under view for this standard type of analysis for parallel design studies usually improves the normal approximation. Based on these analyses, point estimates [least-squares (LS)-means] and exploratory 90% confidence intervals for the strata ratios were calculated by re-transformation of the logarithmic results given by the corresponding ANOVA. The relationship between individual pharmacokinetic or pharmacodynamic parameters and serum albumin or creatinine clearance was investigated by calculating Pearson correlation coefficients.

Results

Study population

Overall, 32 subjects were enrolled into the study and were assigned to one of three groups: healthy ($n = 16$), mild hepatic impairment (Child–Pugh grade A; $n = 8$) and mod-

erate hepatic impairment (Child–Pugh grade B; $n = 8$). The demographic characteristics were similar across the groups, with a mean age of 54.7 years and body mass index of 25.9 kg m^{-2} (Table 1). Subjects with mild hepatic impairment had no ascites or hepatic encephalopathy, and their serum albumin, PT and total bilirubin values were similar to those in the healthy subjects (Table 1). Of the subjects with moderate hepatic impairment, five had small quantities of ascites and four had grade I–II hepatic encephalopathy. Subjects with moderate hepatic impairment had a lower serum albumin concentration (male/female: $3.4/3.8 \text{ g dl}^{-1}$ vs. $4.4/4.3 \text{ g dl}^{-1}$), and higher values for PT (male/female: $16.1/15.3 \text{ s}$ vs. $12.0/12.7 \text{ s}$) and total bilirubin (male/female: $1.9/2.4 \text{ mg dl}^{-1}$ vs. $0.7/0.5 \text{ mg dl}^{-1}$), compared with healthy subjects. Mean creatinine clearance values at screening were lower in subjects with mild hepatic impairment than in healthy subjects or those with moderate hepatic impairment (Table 1).

Pharmacokinetics

Plasma concentrations of rivaroxaban in subjects with mild hepatic impairment were similar to those observed in healthy subjects. However, subjects with moderate hepatic impairment had a higher $C_{\max}$ of rivaroxaban and a prolonged elimination phase (Figure 1). AUC was only increased slightly and $C_{\max}$ was relatively unaffected in subjects with mild hepatic impairment compared with healthy subjects (Table 2). By contrast, in subjects with moderate hepatic impairment AUC and $C_{\max}$ values were increased by 2.27- and 1.27-fold, respectively, compared with healthy subjects (Table 2). Consequently, ANOVA showed AUC to be significantly increased ($P < 0.0004$) in those with moderate hepatic impairment vs. healthy subjects. Women

Figure 1

Rivaroxaban plasma concentration–time curves on a semi-log scale in healthy subjects and subjects with mild hepatic impairment (Child–Pugh grade A, $n = 8$) or moderate hepatic impairment (Child–Pugh grade B, $n = 8$) after administration of a single 10 mg dose of rivaroxaban. The results are shown as mean values $\pm$ SD. $-\triangle-$, healthy subjects; $-\square-$, mild hepatic impairment; $-\bullet-$, moderate hepatic impairment

(both healthy subjects and those with hepatic impairment) had significantly higher $C_{\max}$ values than men ($P < 0.01$, data not shown), which is consistent with previous findings [29]. In addition, $t_{1/2}$ was prolonged by approximately 2 h in subjects with mild or moderate hepatic impairment compared with healthy subjects (Table 2).

The f_u was not consistently altered by hepatic impairment. f_u accounted for 7.9%, 6.2% and 8.8% of total rivaroxaban in healthy subjects, subjects with mild hepatic impairment and those with moderate hepatic impairment, respectively (Table 2). Unbound rivaroxaban concentrations depended mainly on total rivaroxaban concentrations. Statistical analysis of the pharmacokinetic characteristics of unbound rivaroxaban demonstrated a significant effect of hepatic impairment ($P < 0.0001$) on unbound plasma concentrations (AUC_u) and a significant gender effect ($P < 0.05$) on $C_{\max}$ after single-dose administration based on unbound plasma concentrations ($C_{\max,u}$), similar to those observed for total rivaroxaban. The correlation between f_u and serum albumin was significant ($P = 0.0086$), but it was weak and not significant for f_u and total bilirubin ($P = 0.1818$).

The CL/F of rivaroxaban was 6.6 l h^{-1} for healthy subjects, 5.7 l h^{-1} for subjects with mild hepatic impairment and subjects with 2.8 l h^{-1} for moderate hepatic impairment (Table 2). These values were driven not only by the anticipated deterioration in non-renal (hepatic) clearance, but also by a lower CL_R of 1.4 l h^{-1} and 0.7 l h^{-1} in subjects with mild and moderate hepatic impairment, respectively, compared with healthy subjects (2.4 l h^{-1} , Table 2). This was independent of renal function as assessed via creatinine

clearance. Urine collection over a 48 h period showed that the amount of unchanged rivaroxaban excreted via urine in subjects with hepatic impairment was lower than in healthy subjects (25% vs. 36% of the dose).

Pharmacodynamics

Subjects with mild hepatic impairment had similar baseline Factor Xa activity levels to healthy subjects (median 0.84 U ml^{-1} and 0.87 U ml^{-1} , respectively), whereas those with moderate hepatic impairment had lower baseline Factor Xa activity (median 0.63 U ml^{-1}). Rivaroxaban inhibited Factor Xa activity, and there was no relevant difference in inhibition of Factor Xa activity between healthy subjects and those with mild hepatic impairment (Figure 2A, Table 3). By contrast, subjects with moderate hepatic impairment had an increased $AUC(0, t_n)$ and $E_{\max}$ with LS-means ratios of 2.59 and 1.24, respectively, vs. healthy subjects (Figure 2A, Table 3). The results of the ANOVA showed that the differences between subjects with moderate hepatic impairment and healthy subjects and those with mild hepatic impairment were statistically significant for $AUC(0, t_n)$ ($P < 0.01$) and $E_{\max}$ ($P < 0.05$). The increase in $AUC(0, t_n)$ was the result of a more sustained response to rivaroxaban, with inhibition of Factor Xa activity of 28% after 24 h in subjects with moderate hepatic impairment compared with 4% in healthy subjects. There was a weak correlation between inhibition of Factor Xa activity and serum albumin (Pearson correlation coefficients were -0.51 for $AUC(0, t_n)$ and -0.39 for $E_{\max}$). No correlation was observed between inhibition of Factor Xa activity and creatinine clearance.

Baseline PT values were similar between healthy subjects and subjects with mild hepatic impairment, but were higher for subjects with moderate hepatic impairment (Table 1). After the administration of a single 10 mg dose of rivaroxaban, PT prolongation was similar in healthy subjects and those with mild hepatic impairment, but was more pronounced in subjects with moderate hepatic impairment (Figure 2B, Table 3). ANOVA revealed a statistically significant difference between the group with moderate hepatic impairment and healthy subjects for $AUC(0, t_n)$ ($P < 0.0004$) and $E_{\max}$ ($P < 0.0001$). Compared with healthy subjects, those with moderate hepatic impairment had higher values for $AUC(0, t_n)$ (2.14-fold) and $E_{\max}$ (1.41-fold) of PT prolongation. There was a weak inverse correlation between PT prolongation and serum albumin in subjects with moderate hepatic impairment for $AUC(0, t_n)$ and $E_{\max}$ (increases in Pearson correlation coefficients -0.48 and -0.59 , respectively).

The impact of impaired hepatic function on activated partial thromboplastin time and HepTest® was similar to the effect described for PT. Rivaroxaban had no direct effect on ecarin-induced thrombin activity or on anti-thrombin III activity (in plasma) in any of the study groups (data not shown).

Table 2

Pharmacokinetic parameters of rivaroxaban after the administration of a single oral 10 mg dose to healthy subjects and subjects with mild or moderate hepatic impairment

	Healthy subjects (n = 16)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)
AUC ($\mu\text{g l}^{-1} \text{ h}$)	1516 (33.4)	1746 (42.4)	3510 (59.1)
AUC LS-means (90% CI) vs. healthy subjects*	–	1.15 (0.85, 1.57)	2.27 (1.68, 3.07)
C_{max} ($\mu\text{g l}^{-1}$)	213.8 (36.8)	202.6 (41.8)	279.0 (45.8)
C_{max} LS-means (90% CI) vs. healthy subjects*	–	0.97 (0.75, 1.25)	1.27 (0.99, 1.63)
$t_{1/2}$ (h)	8.0 (44.2)	10.4 (82.5)	10.1 (33.9)
t_{max} (h)†	2.0 (1.0–4.0)	2.0 (1.0–4.0)	3.0 (1.0–4.0)
f_u (%)	7.9 (27.8)	6.2 (29.4)	8.8 (52.3)
$\text{Ae}_{\text{ur}}(0-48 \text{ h})$ (%)‡	36.1 (7.7)	24.9 (9.3)	25.1 (12.8)
CL/F (l h^{-1})	6.6 (33.4)	5.7 (42.4)	2.8 (59.1)
CL_R (l h^{-1})	2.4 (38.3)	1.4 (76.7)	0.7 (138.5)

Data are presented as geometric mean (% coefficient of variation) unless indicated otherwise. $\text{Ae}_{\text{ur}}(0-48 \text{ h})$, amount of rivaroxaban excreted in the urine; AUC, area under the plasma concentration–time curve; CI, confidence interval; CL/F , total body clearance of rivaroxaban from plasma; CL_R , renal clearance of rivaroxaban; C_{max} , maximum concentration in plasma; f_u , fraction of unbound rivaroxaban in plasma; LS, least squares; $t_{1/2}$, half-life associated with terminal slope; t_{max} , time to reach C_{max} . *Calculated by analysis of variance. †Median (range). ‡ $\text{Ae}_{\text{ur}}(0-48 \text{ h})$, amount of rivaroxaban excreted in the urine [between rivaroxaban administration and time of last observation (48 h)] expressed as arithmetic mean percentages.

Pharmacokinetic–pharmacodynamic correlation

Linear regression analysis showed a correlation between rivaroxaban plasma concentration (for both total and unbound rivaroxaban) and PT for each individual. In healthy subjects and those with moderate hepatic impairment, the mean individual slopes of the correlation were $0.031 \pm 0.007 \text{ s } (\mu\text{g l}^{-1})^{-1}$ and $0.078 \pm 0.041 \text{ s } (\mu\text{g l}^{-1})^{-1}$ for PT vs. total plasma rivaroxaban concentration, and $0.400 \pm 0.127 \text{ s } (\mu\text{g l}^{-1})^{-1}$ and $0.931 \pm 0.387 \text{ s } (\mu\text{g l}^{-1})^{-1}$ for PT vs. unbound plasma rivaroxaban concentration, respectively. The slope of the regression line was significantly increased in subjects with moderate hepatic impairment compared with healthy subjects, indicating a more pronounced pharmacodynamic response as shown by PT prolongation. This finding was more pronounced for the correlation between PT and unbound rivaroxaban concentrations (Figure 3).

Safety and tolerability

Overall, 10 subjects reported 11 treatment-emergent adverse events. With the exception of one subject who experienced a moderate headache, all adverse events were mild and resolved by completion of the trial. In total, only four adverse events (all headaches) were considered to be possibly related to the study medication. The other adverse events included one case each of headache and thrombophlebitis in two subjects with moderate hepatic impairment, and nasopharyngitis in a healthy subject. No clinically relevant increases in laboratory values were attributable to rivaroxaban. There were changes in laboratory values in subjects with mild or moderate hepatic impairment at baseline, which were considered to be due to the underlying hepatic disease. There were no relevant changes in vital signs or ECG parameters.

Discussion

The liver plays an important role in the clotting process. Consequently, liver diseases (e.g. cirrhosis) and impaired liver function are often associated with coagulation disorders that can be linked, for example, to decreased synthesis of clotting factors including the vitamin K dependent clotting factors II, VII, IX and X [30]. The direct Factor Xa inhibitor rivaroxaban is eliminated via both renal and hepatic pathways, and we have shown in a previous study that rivaroxaban clearance decreases with increasing renal impairment, leading to an increase in rivaroxaban exposure and thus its pharmacodynamic effects [31]. Because approximately two-thirds of the administered rivaroxaban dose undergoes metabolic degradation in the liver [26], the aim of the current study was to determine the influence of the different stages of hepatic impairment on the pharmacokinetics and pharmacodynamics of rivaroxaban.

The results showed that mild hepatic impairment had no apparent influence on the pharmacokinetics of rivaroxaban compared with healthy subjects. By contrast, moderate hepatic impairment resulted in a significant increase in rivaroxaban exposure, as indicated by the higher rivaroxaban plasma concentrations (a 2.27-fold increase in AUC), which was mainly caused by reduced elimination of rivaroxaban, and an increased C_{max} compared with healthy subjects. Studies have shown that chronic liver diseases are associated with variable reductions in CYP activities including CYP3A4 [24]. Because oxidative metabolism catalyzed by CYP3A4 and CYP2J2 is the major hepatic route of rivaroxaban elimination, possible impairment of this pathway in subjects with moderate hepatic impairment may have contributed to the increased rivaroxaban exposure.

Figure 2

Effect of a single dose of rivaroxaban 10 mg on (A) inhibition of Factor Xa activity and (B) prolongation of prothrombin time in healthy subjects ($n = 16$) and subjects with mild hepatic impairment (Child–Pugh grade A, $n = 8$) or moderate hepatic impairment (Child–Pugh grade B, $n = 8$). The results are shown as mean values $\pm$ SD. $\text{---}\blacktriangle\text{---}$, healthy subjects; $\text{---}\blacksquare\text{---}$, mild hepatic impairment; $\text{---}\bullet\text{---}$, moderate hepatic impairment

Furthermore, the results of the present study showed that the marked decrease in total body clearance of rivaroxaban in subjects with moderate hepatic impairment was only partly a result of the expected decrease in non-renal (hepatic) clearance, because there was also a substantial decrease in renal clearance of rivaroxaban. The amount of unchanged rivaroxaban excreted via urine was lower in subjects with hepatic impairment (25% of the dose) than in healthy subjects (36% of the dose). This effect was independent of renal function, assessed via measured creatinine clearance. It is known that hepatic impairment (even to a moderate degree) is associated with a decrease in the

clearance of drugs or active metabolites normally cleared by the kidney. For instance, Villeneuve *et al.* reported that the reduced systemic clearance of cimetidine in cirrhotic patients was mainly caused by the impairment of renal clearance, which was attributed to a decrease in tubular secretion of the unchanged drug [32]. Renal clearance can be influenced by variation in tubular secretion through active transport or by a change in the passive reabsorption rate. Therefore, a possible explanation for the decreased renal clearance of rivaroxaban observed in the current study may be an impairment of active transporter-mediated renal excretion of rivaroxaban owing to underlying hepatic disease. This is further supported by preclinical data in a rat model of acute hepatic failure, which showed that the function of the efflux transport protein P-gp was systemically suppressed, not only in the liver but also in other organs including the kidneys [33]. Thus, the decrease in the transport activity of P-gp in the kidney may contribute to a reduced renal tubular secretion of unchanged drugs, such as rivaroxaban.

In the present study, no relevant differences in pharmacodynamic parameters were observed for mild hepatic impairment classified as Child–Pugh grade A compared with healthy age- and gender-matched subjects. However, cirrhotic subjects classified as Child–Pugh grade B had lower baseline Factor Xa activity levels (0.63 U ml^{-1}) compared with healthy subjects and subjects with mild hepatic impairment (0.87 U ml^{-1} and 0.84 U ml^{-1} , respectively). This is not surprising, because several clotting factors, including Factor X, are synthesized in the liver. Furthermore, inhibition of Factor Xa activity by rivaroxaban was more pronounced in subjects with moderate hepatic impairment compared with both healthy subjects and subjects with mild hepatic impairment, which may be associated with increased rivaroxaban exposure in these subjects, because previous studies have shown that the inhibition of Factor Xa by rivaroxaban was closely correlated with its plasma concentration [9, 10].

The PT assay is a global clotting test that measures the integrity of the extrinsic and final common pathways of coagulation [30]. Changes in several clotting factors that are synthesized in the liver (Factors II, VII, X) affect PT. Therefore, PT is one of five criteria that contribute to the Child–Pugh classification that is used for the evaluation of cirrhotic patients [22].

As expected, no relevant differences in PT prolongation were observed between healthy subjects and subjects with mild renal impairment at baseline and after administration of rivaroxaban. By contrast, a significant increase in PT prolongation was detected in subjects with moderate renal impairment, compared with healthy subjects. In these subjects, the increased sensitivity was also reflected in the correlation between PT and rivaroxaban plasma concentration. The intercept of the linear correlation of PT vs. rivaroxaban plasma concentration (i.e. baseline value for PT without drug) of subjects with moderate hepatic

Table 3

Effect of a single dose of rivaroxaban 10 mg on pharmacodynamic parameters (inhibition of Factor Xa activity and relative prothrombin time prolongation) in healthy subjects and subjects with mild or moderate hepatic impairment

	Healthy subjects (n = 16)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)
Inhibition of Factor Xa activity			
AUC(0,t _n) (% h)	536.5 (54.8)	580.3 (96.9)	1422.0 (32.6)
AUC(0,t _n) LS-means (90% CI) vs. healthy subjects*	–	1.08 (0.70, 1.68)	2.59 (1.69, 3.98)
E _{max} (%)	53.7 (20.4)	52.2 (26.0)	67.8 (15.1)
E _{max} LS-means (90% CI) vs. healthy subjects*	–	0.98 (0.86, 1.13)	1.24 (1.09, 1.42)
Prothrombin time prolongation			
AUC(0,t _n) (x-fold h)	24.7 (38.1)	27.3 (50.4)	53.8 (35.1)
AUC(0,t _n) LS-means (90% CI) vs. healthy subjects*	–	1.06 (0.79, 1.42)	2.14 (1.61, 2.84)
E _{max} (x-fold)	1.6 (13.0)	1.6 (12.0)	2.2 (18.8)
E _{max} LS-means (90% CI) vs. healthy subjects*	–	1.02 (0.93,1.12)	1.41 (1.28, 1.54)

Data are presented as geometric mean (% coefficient of variation) unless indicated otherwise. AUC(0,t_n), area under the effect–time curve between rivaroxaban administration and time of last observation (48 h); CI, confidence interval; E_{max}, maximum effect; LS, least-squares. *Calculated by analysis of variance.

Figure 3

Relationship between unbound rivaroxaban plasma concentrations ($\mu\text{g l}^{-1}$) and the prothrombin time (s) after a single dose of rivaroxaban 10 mg. ---○---, healthy subjects ($n = 16$); ---□---, mild hepatic impairment ($n = 8$); ---+---, moderate hepatic impairment ($n = 8$)

impairment was approximately 3 s higher than in healthy subjects. Slopes of the linear regression analysis between PT and rivaroxaban concentration tended to be steeper for subjects with mild hepatic impairment, and were significantly steeper (>twofold) for subjects with moderate hepatic impairment compared with healthy subjects. The changed sensitivity of PT in relation to drug exposure was even more pronounced when correlating PT with unbound rivaroxaban plasma concentrations (as shown in Figure 3). This is consistent with previous studies showing

that prolongation of PT (with a reagent sensitive to rivaroxaban) was closely correlated with rivaroxaban plasma concentrations [9, 10].

Albumin is the major binding component in human plasma, and concentrations of serum albumin are reduced in patients with liver disease [34]. Plasma protein binding of rivaroxaban is high in humans at approximately 92–95%, with serum albumin being the main binding component [35, 36]. In the present study, protein binding of rivaroxaban was not significantly affected by hepatic

impairment, although two subjects in the moderate hepatic impairment group showed up to a twofold increase in values. The data also showed a weak inverse correlation between serum albumin and AUC and $C_{\max}$ of rivaroxaban plasma concentrations, indicating high AUC and $C_{\max}$ values (and low clearance values) in the presence of low albumin concentrations, mainly driven by the correlation between albumin and hepatic impairment itself. Furthermore, the correlations were closer between serum albumin and unbound rivaroxaban (which was statistically significant) than with total rivaroxaban.

In conclusion, mild impairment of hepatic function in cirrhotic subjects had no impact on rivaroxaban plasma concentrations or pharmacodynamic parameters even though a slight decrease in total body clearance was observed. By contrast, moderate impairment of hepatic function prolonged PT at baseline, which reflects the underlying disease, had a pronounced impact on rivaroxaban total body clearance and increased overall plasma concentrations, leading to more pronounced pharmacodynamic effects (owing to a significantly altered sensitivity in anticoagulant activity in relation to rivaroxaban plasma concentration). These findings suggest that patients with moderate hepatic impairment should not receive rivaroxaban, because these patients have impaired functioning of the coagulation system as a result of the underlying disease, which will increase the risk of bleeding complications. In addition, these patients have a pronounced increase in rivaroxaban systemic exposure, which may be an additional risk factor for an increased bleeding risk.

Competing Interests

All authors have completed the Disclosure of Potential Conflicts of Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare DK, AR, MB, AA, AH, HH and WM had editorial support from Yong-Ling Liu for the submitted work, DK, AR, MB and WM have been employees of Bayer Pharma AG in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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REFERENCES

- Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J* 2006; 27: 1979–2030.
- Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW, American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 381S–453S.
- Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GYH, Manning WJ, American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 546S–92S.
- Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, Guyatt GH, Mark DB, Harrington RA, American College of Chest Physicians. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 776S–814S.
- Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 454S–545S.
- Hawkins D. Limitations of traditional anticoagulants. *Pharmacotherapy* 2004; 24: 62S–5S.
- Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 160S–98S.
- Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JL. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 141S–59S.
- Kubitza D, Becka M, Voith B, Zuehlendorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct Factor Xa inhibitor. *Clin Pharmacol Ther* 2005; 78: 412–21.
- Kubitza D, Becka M, Wensing G, Voith B, Zuehlendorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; 61: 873–80.
- Mueck W, Eriksson BI, Bauer KA, Borris L, Dahl OE, Fisher WD, Gent M, Haas S, Huisman MV, Kakkar AK, Kälebo P, Kwong LM,

- Misselwitz F, Turpie AGG. Population pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct Factor Xa inhibitor – in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet* 2008; 47: 203–16.
- 12 Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. *Clin Pharmacokinet* 2011; 50: 675–86.
- 13 Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W, RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358: 2765–75.
- 14 Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S, RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; 372: 31–9.
- 15 Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AGG, RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358: 2776–86.
- 16 Turpie AGG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD, RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009; 373: 1673–80.
- 17 The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–510.
- 18 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–91.
- 19 Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366: 9–19.
- 20 Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. *Semin Liver Dis* 2002; 22: 83–96.
- 21 Plessier A, Denninger MH, Consigny Y, Pessione F, Francoz C, Durand F, Francque S, Bezeaud A, Chauvelot-Moachon L, Lebrech D, Valla DC, Moreau R. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int* 2003; 23: 440–8.
- 22 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646–9.
- 23 Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. *Scand J Gastroenterol* 1989; 24: 269–76.
- 24 Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol* 2008; 64: 1147–61.
- 25 Lang D, Freudenberger C, Weinz C. *In vitro* metabolism of rivaroxaban – an oral, direct Factor Xa inhibitor – in liver microsomes and hepatocytes of rat, dog and man. *Drug Metab Dispos* 2009; 37: 1046–55.
- 26 Weinz C, Schwarz T, Kubitz D, Mueck W, Lang D. Metabolism and excretion of rivaroxaban, an oral, direct Factor Xa inhibitor, in rats, dogs and humans. *Drug Metab Dispos* 2009; 37: 1056–64.
- 27 Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. *In vitro* and *in vivo* p-glycoprotein transport characteristics of rivaroxaban. *J Pharmacol Exp Ther* 2011; 338: 372–80.
- 28 Rohde G. Determination of rivaroxaban – a novel, oral, direct Factor Xa inhibitor – in human plasma by high-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; 872: 43–50.
- 29 Kubitz D, Becka M, Zuehlendorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. *J Clin Pharmacol* 2007; 47: 218–26.
- 30 Bates SM, Weitz JI. Coagulation assays. *Circulation* 2005; 112: e53–e60.
- 31 Kubitz D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, Lufft V, Wand DD, Philipp T, Bruck H. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2010; 70: 703–12.
- 32 Villeneuve JP, Fortunet-Fouin H, Arsene D. Cimetidine kinetics and dynamics in patients with severe liver disease. *Hepatology* 1983; 3: 923–7.
- 33 Huang ZH, Murakami T, Okochi A, Yumoyo R, Nagai J, Takano M. Expression and function of P-glycoprotein in rats with carbon tetrachloride-induced acute hepatic failure. *J Pharm Pharmacol* 2001; 53: 873–81.
- 34 Rothschild MA, Oratz M, Zimmon D, Schreiber SS, Weiner I, Van Caneghem A. Albumin synthesis in cirrhotic subjects with ascites studied with carbonate-¹⁴C. *J Clin Invest* 1969; 48: 344–50.
- 35 Xarelto® (rivaroxaban): Bayer Pharma AG Summary of Product Characteristics. 2012. Available at http://www.xarelto.com/html/downloads/Xarelto-Prescribing_Information-Nov-2012.pdf (last 3 January 2013).
- 36 Perzborn E, Roehrig S, Straub A, Kubitz D, Mueck W, Laux V. Rivaroxaban: a new oral Factor Xa inhibitor. *Arterioscler Thromb Vasc Biol* 2010; 30: 376–81.