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Effect of Food, an Antacid, and the H₂ Antagonist Ranitidine on the Absorption of BAY 59-7939 (Rivaroxaban), an Oral, Direct Factor Xa Inhibitor, in Healthy Subjects

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To investigate the influence of food and administration of an antacid (aluminum-magnesium hydroxide) or ranitidine on the absorption of BAY 59-7939 (rivaroxaban), 4 randomized studies were performed in healthy male subjects. In 2 food interaction studies, subjects received BAY 59-7939, either as two 5-mg tablets (fasted and fed), four 5-mg tablets (fasted), or one 20-mg tablet (fasted and fed). In 2 drug interaction studies, BAY 59-7939 (six 5-mg tablets) was given alone or with ranitidine (150 mg twice daily, preceded by a 3-day pretreatment phase) or antacid (10 mL). Plasma samples were obtained to assess pharmacokinetic and pharmacodynamic parameters of BAY 59-7939. In the presence of food, time to maximum concentration (t_{\max}) was delayed by 1.25 hours; maximum concentration (C_{\max}) and area under the curve (AUC) were increased, with reduced

interindividual variability at higher doses of BAY 59-7939. Compared with baseline, BAY 59-7939 resulted in a relative increase in maximum prothrombin time (PT) prolongation of 44% (10 mg) and 53% (20 mg) in the fasted state, compared with 53% and 83% after food. Time to maximum PT prolongation was delayed by 0.5 to 1.5 hours after food, with no relevant influence of food type. No significant difference in C_{\max} and AUC was observed with coadministration of BAY 59-7939 and ranitidine or antacid.

Keywords: Direct Factor Xa inhibitor; BAY 59-7939; food; ranitidine; antacid

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Recent anticoagulant research has focused on the identification of synthetic, oral drugs that inhibit key enzymes of the coagulation system, including Factor Xa (FXa), which plays a central role in the coagulation cascade.¹ BAY 59-7939 (rivaroxaban), a novel, oral, direct FXa inhibitor is in clinical development for the prevention and treatment of thromboembolic events (Figure 1). It is a small-molecule, active-site-directed FXa inhibitor. Animal models of venous and arterial thrombosis have shown the antithrombotic

potential of BAY 59-7939.² In recently completed clinical trials in patients undergoing elective total hip and knee replacement, efficacy and safety findings for BAY 59-7939 (2.5-10 mg, twice daily) were comparable with the low-molecular-weight heparin enoxaparin.^{3,4} The pharmacokinetic profile of BAY 59-7939 in healthy subjects is characterized by rapid absorption with a time to peak plasma concentration of 2.5 to 4 hours and a terminal half-life of 5 to 9 hours after multiple doses.⁵

The pharmacokinetics of orally administered drugs, such as vitamin K antagonists, can be sensitive to a number of physiological parameters, including changes in gastric pH, intestinal motility, binding, and chelation, which are frequently precipitated by administration of concomitant drugs or food or both.⁶ Because defining such interactions is particularly important for the development of a new oral anticoagulant,

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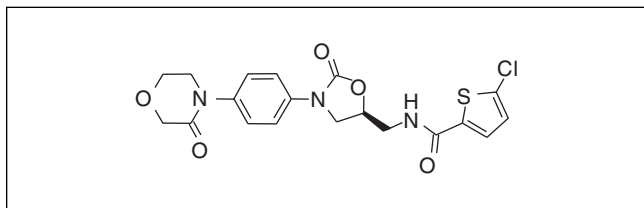


Figure 1. Chemical structure of BAY 59-7939 (5-chloro-N-[[[5S]-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide).

4 studies were undertaken to assess the potential effect of food, an aluminum-magnesium hydroxide antacid, or the histamine H_2 antagonist ranitidine on the pharmacokinetics, pharmacodynamics, and safety of oral BAY 59-7939. The primary aim was to quantify any effect on the absorption of BAY 59-7939.

SUBJECTS AND METHODS

Healthy male subjects, from whom written informed consent was obtained before study enrollment, were included. In the food interaction studies, subjects were aged between 18 and 45 years, with a body mass index (BMI) of 18 to 32 kg/m^2 (18 to 30 kg/m^2 in the BAY 59-7939 single-dose food interaction study). In the drug interaction studies, subjects' ages ranged between 18 and 55 years, with a BMI of 18 to 32 kg/m^2 . All studies were performed in a single center (Bayer HealthCare AG, Pharma Research Center, Wuppertal, Germany), in accordance with the principles of the Declaration of Helsinki, and received approval by the local Ethics Committee of the North-Rhine Medical Council (Ethik-Kommission der Ärztekammer Nordrhein).

A number of factors excluded subjects from participating in the studies, including participation in another clinical trial during the preceding 3 months; recent blood donation; a medical history or findings from the clinical examination that would impair the subjects' ability to participate or complete this study in the opinion of the investigator or the sponsor; regular daily consumption of more than 1 L of usual beer or the equivalent quantity of alcohol, more than 1 L of xanthin-containing beverages, or more than 25 cigarettes; regular use of therapeutic or recreational drugs. Furthermore, subjects were excluded if they had any coagulation disorders, increased bleeding risk, or sensitivity to common causes of bleeding (eg, von Willebrand disease, hemophilia, gastric ulcers). The subjects' baseline characteristics are shown in Table I.

BAY 59-7939 Single-Dose Food Interaction Study

This was a randomized, open-label crossover study, in which 10 subjects were enrolled. Participants received a single, oral dose of BAY 59-7939 as two 5-mg tablets either in the fasted state (at least 10 hours' fast) or in the fed state, administered within 30 minutes after consumption of a standardized high-fat, high-calorie meal (2 large eggs fried in butter, 2 strips of bacon, 2 slices of buttered toast, 125 g hash brown potatoes, and 250 mL whole milk). There was a washout period of at least 1 week before the second treatment period. All subjects were valid for the evaluation of safety; 2 patients were not valid for pharmacokinetic and pharmacodynamic evaluations because of withdrawn consent and treatment cessation due to an adverse event resulting from noncompliance and unrelated to treatment.

BAY 59-7939 Formulation and Food Interaction Study

In this open-label, crossover study, 12 subjects were randomized to receive a single oral dose of four 5-mg BAY 59-7939 tablets in the fasted state (at least 10 hours' fast), a single oral dose of one 20-mg BAY 59-7939 tablet in the fasted state (at least 10 hours' fast) or a single oral dose of one 20-mg BAY 59-7939 tablet in the fed state, administered within 5 minutes of completion of either a standardized high-fat, high-calorie ($n = 6$) (as described) or a high-carbohydrate meal ($n = 6$) (4 slices buttered toast with 50 g jam, 20 g cheese, and sweetened tea). BAY 59-7939 was administered orally with 240 mL of water. A further 250 mL of drinking water was permitted between 2 and 4 hours; after 4 hours, drinking water was provided ad libitum. The study consisted of 3 periods with a 1-week minimum washout between treatments. Two participants were withdrawn, one before any treatment and one because of noncompliance; 11 subjects contributed to the safety assessment of the four 5-mg and one 20-mg BAY 59-7939 tablets in the fasted condition and 10 subjects to the one 20-mg tablet combined with food.

Ranitidine Interaction Study

Twelve subjects were enrolled in this randomized, open-label crossover study. Those randomized to ranitidine (Zantac) received 150 mg twice daily during a 3-day pretreatment phase as outpatients; all patients received a single 30-mg dose of BAY 59-7939 (six 5-mg

Table I Baseline Characteristics of Subjects Administered BAY 59-7939

Parameter	BAY 59-7939 Single-Dose Food Interaction Study (n = 10)	BAY 59-7939 Formulation and Food Interaction Study (n = 12)	Ranitidine Interaction Study (n = 12)	Antacid Interaction Study (n = 12)
Age, median (range), y	33.5 (26-38)	37.0 (19-41)	32.5 (25-39)	35.5 (20-42)
Weight, median (range), kg	85.0 (74-89)	86.0 (76-115)	83.5 (71-91)	86.5 (57-113)
Body mass index, ^a mean (SD)	26.0 (1.8)	26.3 (2.9)	25.1 (2.2)	25.4 (2.7)

a. The body mass index is the weight in kilograms divided by the square of the height in meters.

tablets), under fasted conditions. All subjects were valid for the evaluation of the study primary objectives.

Antacid Interaction Study

This was a randomized, open-label crossover study, in which 12 subjects were enrolled. Participants received BAY 59-7939 as a single 30-mg dose of six 5-mg tablets, under fasted conditions, alone or in conjunction with an aluminum-magnesium hydroxide antacid (Maalox) 10 mL. One participant was withdrawn before any treatment. Eleven subjects were valid for the evaluation of safety and pharmacokinetic and pharmacodynamic parameters.

Sample Collection and Analysis

Pharmacokinetics. Pharmacokinetic parameters were derived from BAY 59-7939 plasma concentration–time profiles obtained by serial blood sampling in all studies. In the 2 food interaction studies, venous blood samples (6 mL) were collected predose and then at 0.25 (omitted in the formulation and food interaction study), 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 24, 36, and 48 hours after study drug administration. In the 2 drug interaction studies, the sampling times at 0.25, 0.75, and 1.25 hours were omitted, with the last sampling time at 72 hours after study drug administration. Blood samples were collected in heparinized tubes and centrifuged at 4°C for 10 minutes at 4000 g; plasma was separated and stored at –15°C until analysis. In addition, in the drug interaction studies, urine samples were collected during the following time periods: 0 to 4, 4 to 8, 12 to 24, 24 to 48, and 48 to 72 hours after drug administration. Urine samples were stored at –15°C and analyzed within 6 weeks of sampling.

Drug assays were performed by Bayer HealthCare AG in the laboratories of the Institute of Clinical Pharmacology, Wuppertal, Germany. Plasma concentrations of BAY 59-7939 were determined using a Sciex API

3000 (PerkinElmer, Boston, Mass) high-performance liquid chromatography tandem mass spectrometry (HPLC/MS/MS) assay. A close chemical analog (BAY 60-4758) was used as internal standard (ISTD). Before HPLC analysis, BAY 59-7939 and ISTD were extracted from the matrix by solid phase extraction using C₁₈ cartridges. Monitored ions were 436 → 145 (BAY 59-7939) and 464 → 145 (ISTD). The validity of the concentration results was verified by assaying quality control (QC) samples produced from blank plasma spiked with known concentrations of BAY 59-7939. In the single-dose food interaction study, for instance, QC samples in the concentration range 1.3 to 808 µg/L were determined with an accuracy of 94.4% to 106% and a precision of 3.1% to 10.1% (n = 22 each). Similar levels of accuracy and precision were achieved in the other studies. The lower limit of quantification (LLOQ) for the assay for BAY 59-7939 in plasma was 0.5 µg/L. All samples were stored below –15°C and analyzed less than 8 weeks after sampling.

In the ranitidine and antacid studies, quantitative analysis of BAY 59-7939 in urine was also performed using the sample preparation procedure described above and HPLC assay but employing ultraviolet detection. The calibration range was 0.01 to 5.26 mg/L. Quality control samples in the concentration range from 0.03 to 4.0 mg/L were determined with an accuracy of 98.6% to 105% and a precision of 1.92% to 5.08% (n = 6 for each). All samples were stored at –15°C and analyzed within 6 weeks after sampling.

Plasma pharmacokinetic parameters (area under the curve [AUC], maximum concentration [C_{max}], time to maximum concentration [t_{max}], and elimination half-life [t_{1/2}]) for BAY 59-7939 were calculated using noncompartmental methods by KINCALC (Bayer HealthCare AG; Wuppertal, Germany). The linear-logarithmic trapezoidal method was used to calculate AUC, and t_{1/2} was calculated by linear least squares regression after logarithmic transformation of the terminal concentrations. C_{max} and AUC values were weight

Table II Pharmacokinetic Parameters After Single Oral Doses of BAY 59-7939 (10 mg), Administered Either Alone or With Food

Parameter	Fasted (n = 8)	Fed (n = 8)	Mean Ratio ^a and 90% CI
AUC _{0-∞} , µg·h/L	888 (24)	1107 (27)	1.28 (1.15-1.43)
C _{max} , µg/L	113 (27)	158 (23)	1.41 (1.20-1.66)
t _{max} , median (range), h	2.75 (0.75-4.0)	4.0 (3.0-4.0)	
t _{1/2} , h	6.64 (24)	6.15 (38)	

Unless otherwise indicated, values are shown as geometric mean with percentage coefficient of variation (%CV) in parentheses. CI, confidence interval; AUC_{0-∞}, area under the drug plasma concentration–time curve from time 0 to infinity; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; t_{1/2}, terminal elimination half-life.

a. Calculated by analysis of variance.

adjusted (C_{max, norm} and AUC_{norm}) according to the dose in milligrams per kilogram. Plasma concentration–time courses of BAY 59-7939 (calculated if two thirds or more of individual values were greater than the LLOQ) are presented as geometric mean values. For calculation of the mean value, data points below the LLOQ were substituted by 50% of this limit. The amount of BAY 59-7939 excreted in the urine was used to determine the renal clearance (CL_R).

Pharmacodynamics. The pharmacodynamic effects of BAY 59-7939 were assessed primarily by evaluation of FXa activity (measured directly) and prothrombin time (PT). Plasma samples were stored, as described, until analysis at the Biomarker and Pharmacogenetics Laboratory at Bayer HealthCare AG. Prothrombin time (performed using freeze-dried thromboplastin from rabbit brain [Neoplastin Plus; Roche Diagnostics, Mannheim, Germany]) was measured with a ball coagulometer KC 10 (Amelung, Lemgo, Germany), according to the manufacturer's instructions. After sample dilution, FXa activity was determined by a photometric assay (Chromogenix, Milan, Italy; method based on supplier's instructions). Concentrations greater than 0.1 IU/mL (the LLOQ) were determined with a precision of 9.5% to 14% and an accuracy of 99.5% to 114%. In addition, the action of BAY 59-7939 was evaluated by measurement of Factor IIa (FIIa) and antithrombin (AT) activity, as previously described.⁷

Statistical Analysis

Descriptive statistical methods were used for safety as well as pharmacodynamic and pharmacokinetic data. Statistical analysis of AUC from time 0 to infinity (AUC_{0-∞}) and C_{max} was based on an analysis of variance (ANOVA) model. To compare pharmacokinetics between treatments, retransformation of the logarithms of AUC_{0-∞} and C_{max} were analyzed using

ANOVA including subject, sequence, period, and treatment effects. Based on these analyses, point estimates and exploratory 90% confidence intervals (CI) for the treatment ratios were calculated. No interaction was concluded if the 90% CI for the treatment ratios fell within the range 0.80 to 1.25. The statistical evaluation was performed using SAS version 6 (SAS Institute, Cary, NC) software package.

RESULTS

BAY 59-7939 Single-Dose Food Interaction Study

Pharmacokinetics. Under fasted conditions, there was a prompt increase in the plasma concentration of BAY 59-7939 (median t_{max}, 2.75 hours) (Table II). In the fed state, t_{max} increased to 4.0 hours, indicative of slower absorption (Figure 2). Geometric mean AUC_{0-∞} (888 ng·h/mL [fasted] and 1107 ng·h/mL [fed]) and C_{max} (113 µg·h/mL [fasted] and 158 µg·h/mL [fed]) both significantly increased with the administration of food (*P* < .05). The geometric mean ratio (fed vs fasted) of AUC_{0-∞} (90% CI) for BAY 59-7939 was 1.28 (1.15-1.43), and for C_{max}, the ratio was 1.41 (1.20-1.66), indicating increases of approximately 28% and 41%, respectively. Individual variability was moderate and similar between fasted and fed subjects. The terminal half-life remained almost unchanged (6.1 hours [fed] and 6.6 hours [fasted]).

Pharmacodynamics. After consumption of food, maximum PT prolongation increased, from a factor of 1.44 (fasted state) over baseline to 1.53 (fed) (Table III). Time to maximal PT prolongation was delayed by about 1.5 hours (from 2.5 hours to 4.0 hours) after a meal (Figure 3), returning to the normal range after approximately 24 hours. The changes seen in inhibition of FXa activity were similar (Figure 4).

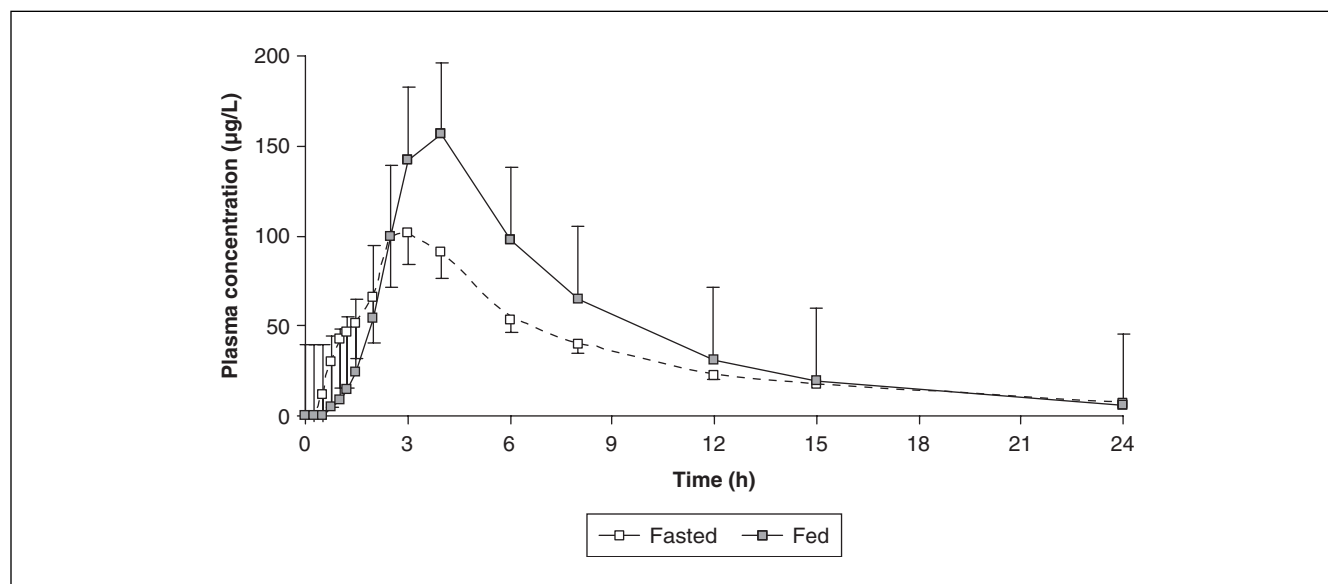


Figure 2. Plasma concentration-time profiles with or without a high-fat, high-calorie meal. Values are geometric means (SD) for $n = 8$.

Table III Pharmacodynamic Parameters After Single Oral Doses of BAY 59-7939 Administered Either Together With Food, Ranitidine, or Antacid

Parameter	Food Interaction Study ^a BAY 59-7939 (2 × 5-mg tablets)		Ranitidine Interaction Study ^b BAY 59-7939 (6 × 5-mg tablets)		Antacid Interaction Study ^b BAY 59-7939 (6 × 5-mg tablets)	
	Fasted (n = 8)	Fed (n = 8)	Alone (n = 12)	Plus Ranitidine (n = 12)	Alone (n = 11)	Plus Antacid (n = 11)
Maximum PT prolongation, relative increase	1.44 (1.30-1.52)	1.53 (1.37-1.72)	1.63 (1.37-2.10)	1.67 (1.30-2.45)	1.58 (1.40-1.90)	1.54 (1.36-2.10)
Maximum inhibition of FXa activity, %	33.6 (18-42)	42.5 (35-51)	48.4 (36-70)	49.4 (33-74)	48.5 (38-58)	43.8 (31-56)

PT, prothrombin time; FXa, Factor Xa.

a. Arithmetic mean (range).

b. Geometric mean (range).

BAY 59-7939 was specific for FXa and had no effect on FIIa and AT activity.

BAY 59-7939 Formulation and Food Interaction Study

Pharmacokinetics. No relevant pharmacokinetic differences were noted when 20 mg BAY 59-7939 was administered either as four 5-mg tablets or as a single 20-mg tablet in the fasted state (Table IV). The weight-adjusted ratios (20 mg vs 4 × 5 mg) of $AUC_{0-\infty}$ and C_{max} (90% CI) were 0.97 (0.88-1.08) and 1.04 (0.92-1.17), respectively.

Administration of a single 20-mg BAY 59-7939 tablet with food resulted in t_{max} increasing from 2.75 hours to 4 hours (Figure 5). Similarly, the AUC and C_{max} were significantly higher after food. The weight-adjusted geometric mean ratios (fed/fasted) of $AUC_{0-\infty}$ and C_{max} (90% CI) were 1.23 (1.11-1.37) and 1.74 (1.54-1.96), respectively. Individual variability for all pharmacokinetic parameters was lower in fed subjects; the coefficient of variation for $AUC_{0-\infty}$ and C_{max} was reduced from 41% and 33%, respectively, in fasted subjects to 34% and 26%, respectively, in fed subjects.

No significant pharmacokinetic differences between a high-fat, high-calorie and a high-carbohydrate meal

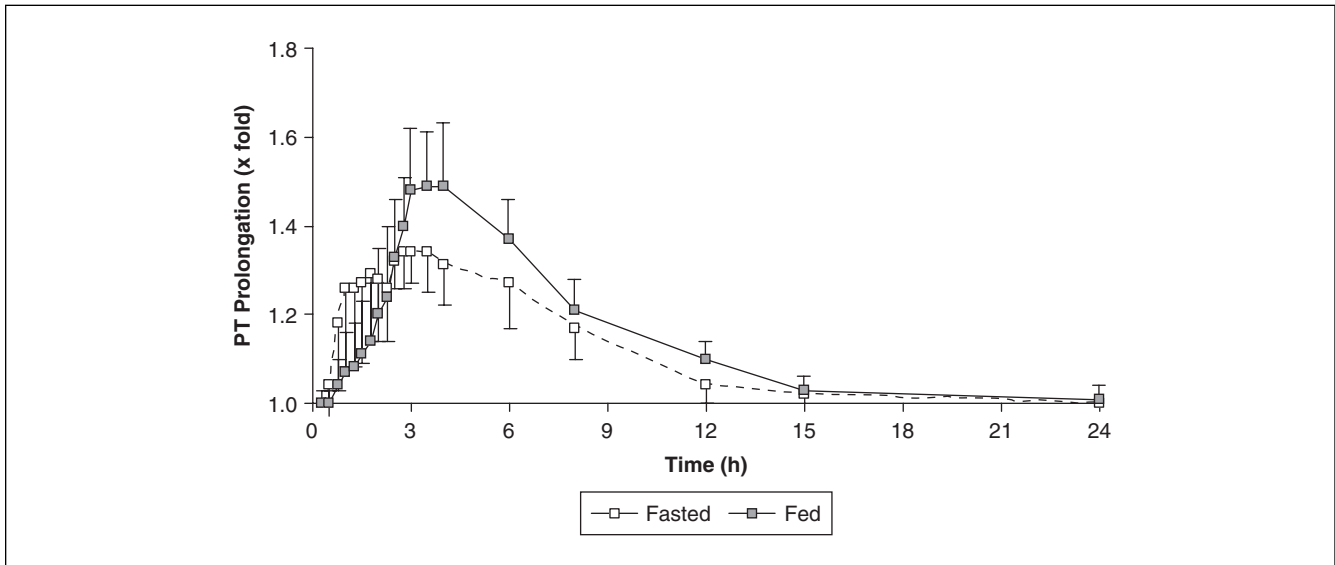


Figure 3. Prothrombin time (PT) versus time profiles with or without a high-fat, high-calorie meal. Values are arithmetic means (SD) for $n = 9$.

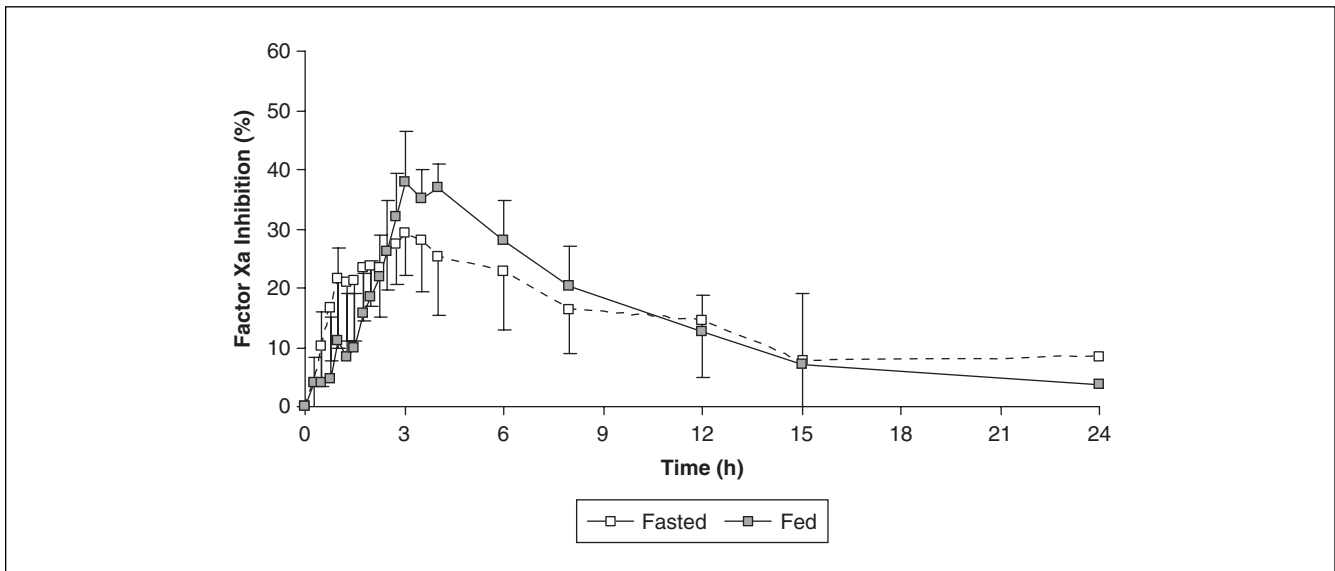


Figure 4. Inhibition of FXa activity versus time profiles with or without a high-fat, high-calorie meal. Values are arithmetic means (SD) for $n = 9$.

were noted (Table V). The weight-adjusted ratios (high-fat, high-calorie vs high-carbohydrate meal) for $AUC_{0-\infty}$ and C_{max} (90% CI) were 0.92 (0.75-1.14) and 1.07 (0.84-1.36), respectively.

Pharmacodynamics. Compared with baseline, the relative increase in maximum PT prolongation was

1.53 in the fasted state, compared with 1.83 after food; maximum PT prolongation was reached 2.5 hours (fasted) and 3 hours (fed) after administration of BAY 59-7939. Inhibition of FXa activity with the 20-mg BAY 59-7939 tablet was most pronounced when given with food compared with the fasted state (maximum inhibition 51% vs 34%), and the maximum

Table IV Pharmacokinetic Parameters After Single Oral Doses of BAY 59-7939 20 mg, Administered Either as Four 5-mg Tablets or One 20-mg Tablet, Either Alone or With Food

Parameter	Drug Dosage Administered		
	4 × 5-mg Tablets	20-mg Tablet	
	Fasted (n = 10)	Fasted (n = 10)	Fed (n = 10)
AUC _{0-∞} , µg·h/L	1678 (41)	1629 (41)	2021 (34)
AUC _{0-∞,norm} , g·h/L	7521 (34)	7301 (31)	9058 (26)
C _{max} , µg/L	153 (33)	158 (33)	273 (26)
C _{max,norm} , g/L	684 (26)	709 (26)	1226 (19)
t _{max} , median (range), h	1.25 (0.75-4.0)	2.25 (0.75-4.0)	3.50 (1.25-6.0)
t _{1/2} , h	9.29 (60)	9.12 (55)	7.02 (30)
AUC _{0-∞,norm} ratio 20 mg fasted vs 4 × 5 mg fasted (90% CI) ^a		0.97 (0.88-1.08)	
C _{max,norm} ratio 20 mg fasted vs 4 × 5 mg fasted (90% CI) ^a		1.04 (0.92-1.17)	
AUC _{0-∞,norm} ratio 20 mg fed vs fasted (90% CI) ^a			1.23 (1.11-1.37)
C _{max,norm} ratio 20 mg fed vs fasted (90% CI) ^a			1.74 (1.54-1.96)

Unless otherwise indicated, values are shown as geometric mean with percentage coefficient of variation in parentheses. AUC_{0-∞}, area under the drug plasma concentration-time curve from time 0 to infinity; AUC_{0-∞,norm}, bodyweight- and dose-normalized AUC_{0-∞}; C_{max}, maximum plasma concentration; C_{max,norm}, bodyweight- and dose-normalized C_{max}; t_{max}, time to reach C_{max}; t_{1/2}, terminal elimination half-life; CI, confidence interval.
a. Calculated by analysis of variance.

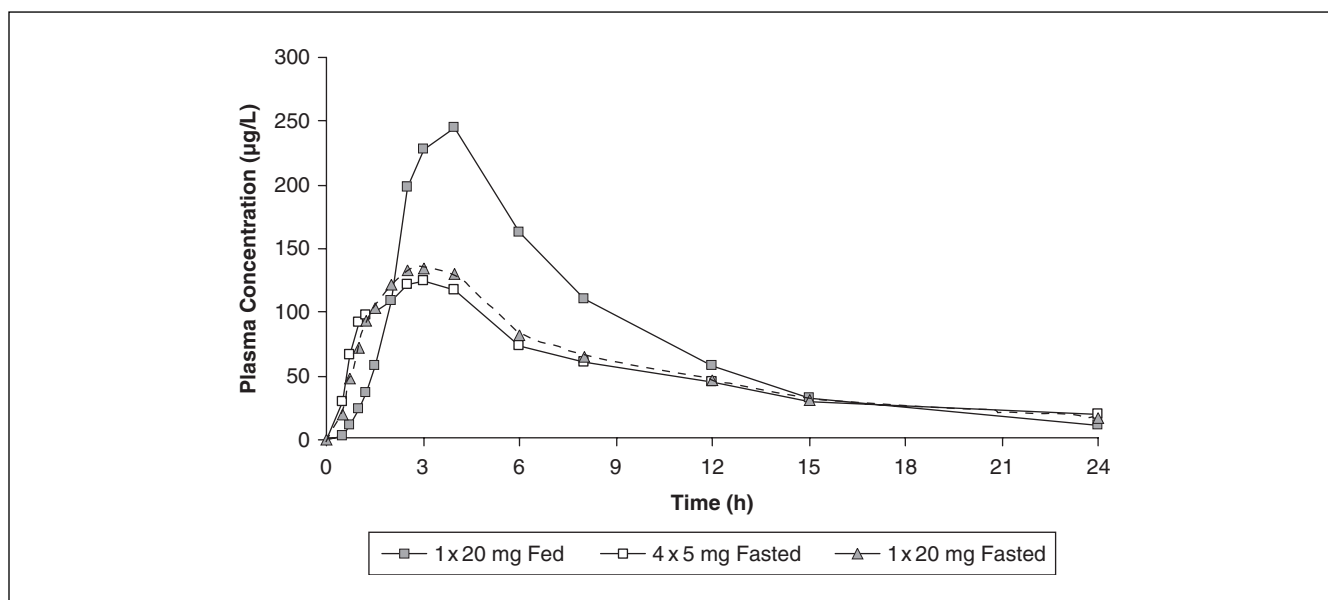


Figure 5. Plasma concentration-time profiles after administration either as four 5-mg tablets or one 20-mg tablet, with and without food. Values are geometric means for n = 10.

effect was delayed by about 1.5 hours (from 2.5 hours to 4 hours).

Ranitidine Interaction Study

Pharmacokinetics. The change in gastric pH by pretreatment with ranitidine had no effect on the

plasma-concentration profiles of BAY 59-7939 (Table VI). The 90% CI (0.85-1.20) surrounding the geometric ratio of AUC_{0-∞} (with vs without ranitidine) was covered by the generally accepted range for the assumption of equal bioavailability (0.80-1.25). The 90% CI for C_{max} (0.78-1.50) fell slightly outside this accepted interval.

Table V Pharmacokinetic Parameters After Single Oral Doses of BAY 59-7939 20 mg Administered With Either a High-Fat, High-Calorie or High-Carbohydrate Meal

Parameter	High-Fat, High-Calorie Meal (n = 6) ^a	High-Carbohydrate Meal (n = 4) ^b	Mean Ratio (90% CI) ^c
AUC _{0-∞} , µg·h/L	1990 (16)	2068 (56)	
AUC _{0-∞,norm} , g·h/L	8458 (13)	10039 (39)	0.92 (0.75-1.14)
C _{max} , µg/L	273 (17)	275 (40)	
C _{max,norm} , g/L	1159 (10)	1333 (28)	1.07 (0.84-1.36)
t _{max} , median (range), h	4.0 (1.25-6.0)	3.0 (2.5-4.0)	
t _{1/2} , h	7.92 (26)	5.85 (28)	

Unless otherwise indicated, values are shown as geometric mean with percentage coefficient of variation in parentheses. CI, confidence interval; AUC_{0-∞}, area under the drug plasma concentration-time curve from time 0 to infinity; AUC_{0-∞,norm}, bodyweight- and dose-normalized AUC_{0-∞}; C_{max}, maximum plasma concentration; C_{max,norm}, bodyweight- and dose-normalized C_{max}; t_{max}, time to reach C_{max}; t_{1/2}, terminal elimination half-life.

a. Given as an American breakfast.

b. Given as a continental breakfast.

c. Calculated by analysis of variance.

Table VI Pharmacokinetic Parameters After Single Oral Doses of BAY 59-7939 30 mg Administered With Either Ranitidine or Antacid

Parameter	Ranitidine Interaction Study BAY 59-7939 (6 × 5-mg Tablets)		Antacid Interaction Study BAY 59-7939 (6 × 5-mg Tablets)	
	Alone (n = 12)	Plus Ranitidine (n = 12)	Alone (n = 11)	Plus Antacid (n = 11)
AUC _{0-∞} , µg·h/L	1741 (26)	1763 (39)	1828 (18)	1734 (21)
C _{max} , µg/L	176.18 (38)	191 (44)	205 (15)	177.7 (32)
t _{max} , median (range), h	2.0 (1.0-4.0)	2.0 (0.5-6.0)	2.5 (1.0-4.0)	4.0 (0.5-4.0)
t _{1/2} , (range), h	8.39 (27)	8.54 (37)	8.56 (42)	7.26 (37)
CL _R , L/h	2.81 (36)	2.59 (34)	2.71 (24)	3.02 (30)
AUC _{0-∞} ratio with vs without (90% CI) ^a		1.01 (0.85-1.20)		0.95 (0.83-1.08)
C _{max} ratio with vs without (90% CI) ^a		1.08 (0.78-1.50)		0.87 (0.73-1.03)

Unless otherwise indicated, values are shown as geometric mean with percentage coefficient of variation in parentheses. AUC_{0-∞}, area under the drug plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; t_{1/2}, terminal elimination half-life; CL_R, renal clearance; CI, confidence interval.

a. Calculated by analysis of variance.

Pharmacodynamics. PT prolongation was comparable between BAY 59-7939 alone (relative mean increase of 1.63 times baseline) and when given with ranitidine (1.67 times baseline increase). Maximal inhibition of FXa activity was comparable between BAY 59-7939 alone (mean 48%) and in combination with ranitidine (49%), returning to normal after approximately 24 hours (Table III).

Antacid Interaction Study

Pharmacokinetics. Treatment with the antacid had no effect on the plasma concentration–time profile. The 90% CI (0.83-1.08) surrounding the geometric mean ratio of AUC_{0-∞} (with vs without antacid) was within the generally accepted range for the assumption of

equal bioavailability (0.8-1.25) (Table VI). The 90% CI for C_{max} (0.73-1.03) fell slightly below the interval.

Pharmacodynamics. Maximal PT prolongation was comparable; the relative increase in the geometric mean was 1.58 times baseline after BAY 59-7939 alone and 1.54 times baseline when given in combination with antacid (Table III). Similar between-treatment findings were noted for maximal inhibition of FXa activity (48.5% after BAY 59-7939 alone and 43.8% in combination).

Safety and Tolerability

BAY 59-7939 was well tolerated in all studies, with a low incidence of adverse events. There were no

serious adverse events; no subjects discontinued because of treatment-related adverse events. In all studies, no relevant changes were observed in blood pressure, heart rate, 12-lead electrocardiogram, or clinical laboratory measurements, during the study or follow-up period, compared with baseline.

In the single-dose food interaction study, 2 adverse events were reported in 2 subjects. Both events were considered unrelated to study drug. One subject was excluded because of high creatine kinase values secondary to physical activity before the start of the second period.

In the formulation and food interaction study, there were 12 adverse events, with no differences between the 3 groups; all events were of mild or moderate intensity. Drug-related adverse events ($n = 4$) were headache and shoulder pain. Adverse events unrelated to study drug included common cold, sore throat, and fever.

In the ranitidine interaction study, there were 8 adverse events, 4 occurring after administration of BAY 59-7939 alone and in combination with ranitidine. None were related to study drug. The events were common cold, headache, and nausea accompanied by insomnia.

In the antacid interaction study, 2 subjects administered BAY 59-7939 plus antacid reported loose stools and unusual catheter-site bleeding, which were thought to be possibly related to the study drug.

DISCUSSION

These studies demonstrate that absorption of orally administered BAY 59-7939 was moderately increased by administration of food to healthy male subjects, elimination remaining unaffected. Reduced interindividual variability in pharmacokinetic parameters was noted in fed subjects treated with a higher dose of BAY 59-7939. Furthermore, absorption of BAY 59-7939 was unaltered by the concomitant administration of 2 drugs that alter intestinal pH, namely ranitidine and an antacid. BAY 59-7939 was well tolerated in all subjects.

Administration of BAY 59-7939 with food increased the AUC and C_{\max} compared with the fasted state. The relative increases for AUC and C_{\max} differed; they were in the region of 25% for AUC, and for C_{\max} , were between 41% and 74% for the 10-mg and 20-mg doses, respectively. When BAY 59-7939 was administered as a single 20-mg dose, the coefficient of variation seen in peak plasma concentration and AUC was lower in fed subjects, compared with those in the

fasted state. A mean delay to reach maximal concentration of BAY 59-7939 of 1.5 hours was observed. Both meal types resulted in increased but delayed maximum plasma concentrations of approximately the same magnitude, although the small sample size suggests that these results should not be regarded as definitive. In all studies, the $t_{1/2}$ was unchanged, ranging from 6 to 9 hours. This food effect is in line with previous findings reported with BAY 59-7939. In a multiple-dose escalation study of BAY 59-7939 (5 mg once daily to 30 mg twice daily) in 68 subjects in the fed state, C_{\max} occurred after 2.5 to 4 hours, with $t_{1/2}$ of approximately 5 to 9 hours.⁵ In comparison, in a single-dose escalation study in fasted subjects (1.5-80 mg), t_{\max} was reached after 2 hours.⁷

The comparison of BAY 59-7939, given either as a single 20-mg tablet or four 5-mg tablets in the fasted state, showed that both dosing regimens resulted in similar pharmacokinetic effects. This finding suggests that the dissolution of BAY 59-7939 is similar, irrespective of the strength of dose contained in each tablet, and also that the rate of subsequent absorption is similar.

Generally, the pharmacokinetic findings were reflected in the pharmacodynamic parameters assessed; in particular, with food there was an increased and delayed PT prolongation with corresponding changes in inhibition of FXa activity after BAY 59-7939 administration. The findings in previous studies^{4,5} of a close correlation between the pharmacodynamic effects and plasma concentrations of BAY 59-7939, with dose-dependent and predictable effect-time profile for PT prolongation, suggest that this pharmacodynamic parameter may be suitable to employ in clinical trials as an assessment of drug exposure.

Food effects are not uncommon and occur because of diverse factors regulating oral bioavailability and food interaction. For instance, the observed lag time in absorption of approximately 1 hour in both food interaction studies is quite common, reflecting prolonged length of stay in the stomach for the drug formulation secondary to reduced gastric motility after a meal.^{8,9} The increase in rate and extent of absorption seen in these studies in the fed state may well relate both to the lipophilicity and limited aqueous solubility of BAY 59-7939.

No evidence of a relevant difference in the absorption of BAY 59-7939 30 mg alone or in combination with ranitidine or antacid was noted. These findings suggest that the absorption and bioavailability of BAY 59-7939 is not adversely affected by changes in gastric pH. Again, the pharmacokinetic findings were reflected in the pharmacodynamic parameters

assessed; in particular, there was little difference in the PT prolongation, maximum inhibition of FXa activity, and time to maximum inhibition between subjects given BAY 59-7939 alone and in combination with ranitidine or antacid. This finding is important to establish, as patients undergoing surgery frequently experience gastric disturbances in the postoperative period and are commonly prescribed antacid medications, such as those investigated.

BAY 59-7939 was well tolerated in all 4 studies, regardless of dose or coadministration of food or other medications altering the gastric pH. In all studies, adverse events were of mild or moderate intensity, with no severe BAY 59-7939-related adverse events described.

The findings of the present studies have been of value in the design of clinical trials of BAY 59-7939. Studies investigating patients undergoing elective total hip or knee replacement,^{3,4} in which BAY 59-7939 was administered in a range of doses, have been reported. In those studies, BAY 59-7939, given within 1 to 2 hours of food, was shown to have a similar efficacy and safety profile to the low-molecular-weight heparin enoxaparin, with an optimal dose range of BAY 59-7939 of 2.5 to 10 mg twice daily reported. In the fasting, postoperative period, the somewhat smaller peak concentrations of BAY 59-7939 under fasted conditions may be somewhat beneficial, given the importance of establishing wound hemostasis early after the completion of surgery.

A strength of this report is that all 4 studies were of a crossover design. The 2-period crossover design was chosen because it allowed for an unbiased comparison between BAY 59-7939 and the combination of BAY 59-7939 and either food, ranitidine, or antacid. The small sample size used in the comparison of the type of meal administered (either high-fat or high-carbohydrate), however, does not allow firm conclusions on the influence of the type of food on corresponding pharmacokinetic parameters.

CONCLUSIONS

The pharmacokinetic and pharmacodynamic characteristics of BAY 59-7939 were moderately altered

by food, resulting in delayed absorption, and in increased peak concentration and prolongation of PT, but were unaffected by changes in gastric pH induced by ranitidine or antacid. The effect of food was most pronounced at the higher dose of BAY 59-7939 investigated. For the lower, 10-mg dose, the difference in absorption seen was close to the moderate levels of interindividual variability found and would not be expected to be of clinical significance. The clinical efficacy and safety evaluation of BAY 59-7939 for the prevention of venous thromboembolism is continuing through a phase III clinical trial program after major orthopaedic surgery (the RECORD studies).

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