

Clinical Pharmacokinetics and Pharmacodynamics of the Oral Direct Thrombin Inhibitor Dabigatran Etexilate

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Abstract

The direct thrombin inhibitor dabigatran etexilate is currently in phase III of development for the prophylaxis and treatment of thromboembolic disorders, with three trials completed in primary venous thromboembolism (VTE) prevention. Dabigatran etexilate is an orally administered prodrug, which is rapidly absorbed and converted to the active form, dabigatran. Dabigatran has been shown to specifically and reversibly inhibit thrombin, the key enzyme in the coagulation cascade. Studies in healthy volunteers and in patients undergoing orthopaedic surgery have indicated that dabigatran has a predictable pharmacokinetic/pharmacodynamic profile, allowing for a fixed-dose regimen. Peak plasma concentrations of dabigatran are reached approximately 2 hours after oral administration in healthy volunteers, with no unexpected accumulation of drug concentrations upon multiple dosing. Excretion is predominantly via the renal route as unchanged drug. Dabigatran is not metabolized by cytochrome P450 isoenzymes. The small differences in dabigatran pharmacokinetics associated with age and gender are attributed to variations in renal function. Additional studies have shown that the pharmacokinetic/pharmacodynamic profile of dabigatran is consistent across a range of patient populations, with no effect of moderate hepatic impairment being observed. Drug-drug interactions are not observed with concomitant administration of atorvastatin, diclofenac or digoxin. The pharmacodynamic profile of dabigatran demonstrates effective anticoagulation combined with a low risk of bleeding. Further phase III studies are ongoing, including acute VTE treatment and stroke prevention in atrial fibrillation; the results obtained so far show that dabigatran etexilate is well tolerated and effective in the treatment and prevention of thromboembolic events.

Thrombin is a plasma serine protease that plays a central role in coagulation and haemostasis. Thrombin is produced by the proteolytic cleavage of prothrombin and catalyses the conversion of

fibrinogen to fibrin, leading to thrombus formation. In pathological conditions, thrombus formation can result in thrombotic complications, which comprise deep-vein thrombosis (DVT), myocar-

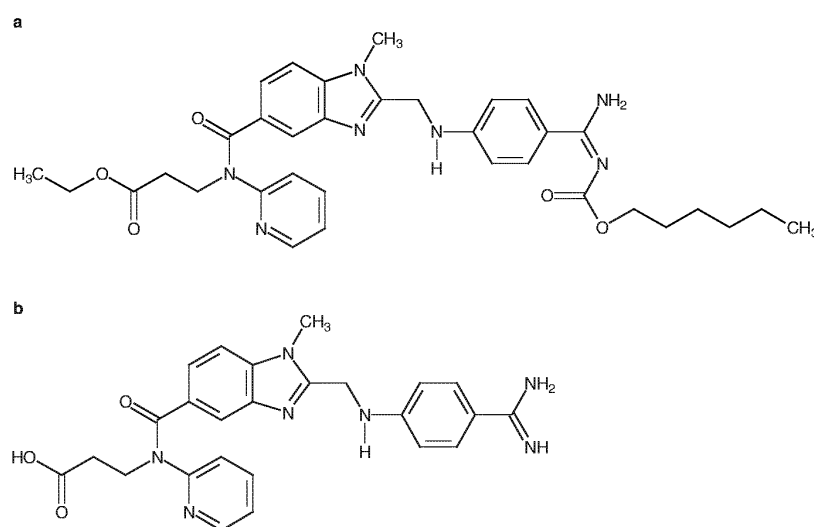


Fig. 1. Chemical structures of (a) dabigatran etexilate (BIBR 1048) and (b) dabigatran (BIBR 953).

dial infarction, cerebrovascular disease and peripheral arterial disease.^[11] Thromboembolic diseases are considered to be a major cause of morbidity and mortality worldwide.^[12]

Parenteral anticoagulants, such as heparin and low-molecular-weight heparins (LMWHs), are the current standards in short-term anticoagulation therapy.^[13] LMWHs reduce many of the undesired effects of heparins, including variable responses due to plasma protein binding, low activity against fibrin-bound thrombi and heparin-induced thrombocytopenia.^[4,5]

Fondaparinux sodium, which indirectly targets Factor Xa, has proved to be highly effective in antithrombotic therapy; however, it appears to be associated with an increased risk of bleeding.^[6] Vitamin K antagonists, such as the coumarin derivative warfarin, have significant limitations due to a nonspecific mechanism of action with a slow onset and offset of action. Warfarin is associated with a plethora of drug-drug interactions. Inhibition of cytochrome P450 (CYP) isoenzymes 2C9/3A4 by concomitant drugs, nutritional vitamin K, or other drug-food interactions result in highly variable warfarin pharmacodynamics.^[7] Mutations in the gene encoding the warfarin target enzyme vitamin K epoxide reductase can cause warfarin resistance, and represent a further source of interindividual variability.^[8] Patients require frequent monitoring of their anticoagulant status due to the narrow therapeutic window of vitamin K antagonists.

Synthetic, small-molecule direct thrombin inhibitors (DTIs) represent a new therapeutic class of antithrombotic agents that have the potential to overcome the above limitations.^[9] By interacting directly and exclusively with the active site of thrombin, univalent DTIs inactivate fibrin-bound thrombin.^[10] Reversible inhibition of thrombin leaves a small amount of free, enzymatical-

ly active thrombin available for control of haemostasis.^[11,12] Ximelagatran, the orally bioavailable prodrug of the active moiety melagatran, was the first oral agent in the new class of reversible DTIs. It was developed to combine oral bioavailability with a more favourable benefit : risk ratio than established antithrombotic drugs.^[13] However, prolonged therapy with ximelagatran resulted in idiosyncratic hepatic toxicity.^[14] Clinical trials were therefore stopped, and ximelagatran was withdrawn from the market.^[15]

Dabigatran etexilate (BIBR 1048) is a DTI prodrug that is orally absorbed and completely converted to the active form dabigatran (BIBR 953) [figure 1]. Dabigatran etexilate was synthesized as a derivative of the peptide-like, benzamidine-based inhibitor *N*- α -naphthylsulphonylglycyl-4-amidinophenylalanine piperidine (NAPAP). The amidine group of dabigatran forms a salt bridge with the carboxylate of aspartate residue Asp189. Hydrophobic interactions are formed by the piperidine ring and the naphthyl moiety with the proximal and distal pocket of the active site of thrombin.^[16] Because of its highly polar, zwitterionic nature, dabigatran is not orally available; therefore, the prodrug of dabigatran, dabigatran etexilate, was developed. Predictable and potent anticoagulant effects were observed after oral administration of dabigatran etexilate in different animal species.

1. Preclinical Studies

Dabigatran inhibits human thrombin in a concentration-dependent manner, with an inhibition constant (K_i 4.5 nmol/L) comparable with melagatran (11.2 ± 0.4 nmol/L), and has been shown to be a competitive inhibitor of thrombin.^[12] Dabigatran displays

highly selective and rapid but reversible binding to thrombin. Reversible binding may contribute towards safer and more predictable anticoagulant treatment than has been observed with irreversible, non-covalent binding, as shown for the first DTI, hirudin.^[17] Thrombin is the most potent physiological agonist of platelet activation and aggregation. Dabigatran potently inhibits platelet aggregation, with a concentration that produces 50% inhibition (IC_{50}) similar to the K_i of thrombin.^[12] In addition, dabigatran inhibits tissue factor-induced thrombin generation in human platelet-poor plasma in a concentration-dependent manner, and decreased endogenous thrombin generation.^[12] Prolongation of blood coagulation times by dabigatran in animal species and human plasma revealed similar patterns, with the thrombin clotting time (TT) and ecarin clotting time (ECT) being the most sensitive clotting assays, followed by the activated partial thromboplastin time (aPTT) and the prothrombin time (PT) [expressed as the international normalized ratio (INR)] (figure 2).^[18] These tests were also employed for assessment of the pharmacological effect of dabigatran during clinical development.

The antithrombotic and anticoagulant effects of dabigatran and its prodrug were investigated in a rabbit model of venous thrombosis. In the rabbit jugular vein, dabigatran reduced thrombus formation in a dose-dependent manner with a dose that produced a 50% effective response (ED_{50}) of 4.65 mg/kg, demonstrating effective antithrombotic activity. Thrombus formation was almost maximally reduced with 10 mg/kg of dabigatran etexilate within 1 hour of pretreatment, indicating a fast onset of action.^[19,20] The preclinical data showed oral dabigatran etexilate to be an effective antithrombotic agent that warranted clinical development for the prophylaxis and treatment of venous thromboembolism (VTE).

This article reviews the clinical pharmacokinetic/pharmacodynamic profile of dabigatran etexilate in clinical studies in healthy volunteers and patients undergoing orthopaedic surgery.

2. Pharmacokinetics

In early phase I clinical trials in healthy volunteers, dabigatran etexilate was administered in tartaric acid solution or as tablets. In the solid oral dosage form intended to be marketed, dabigatran

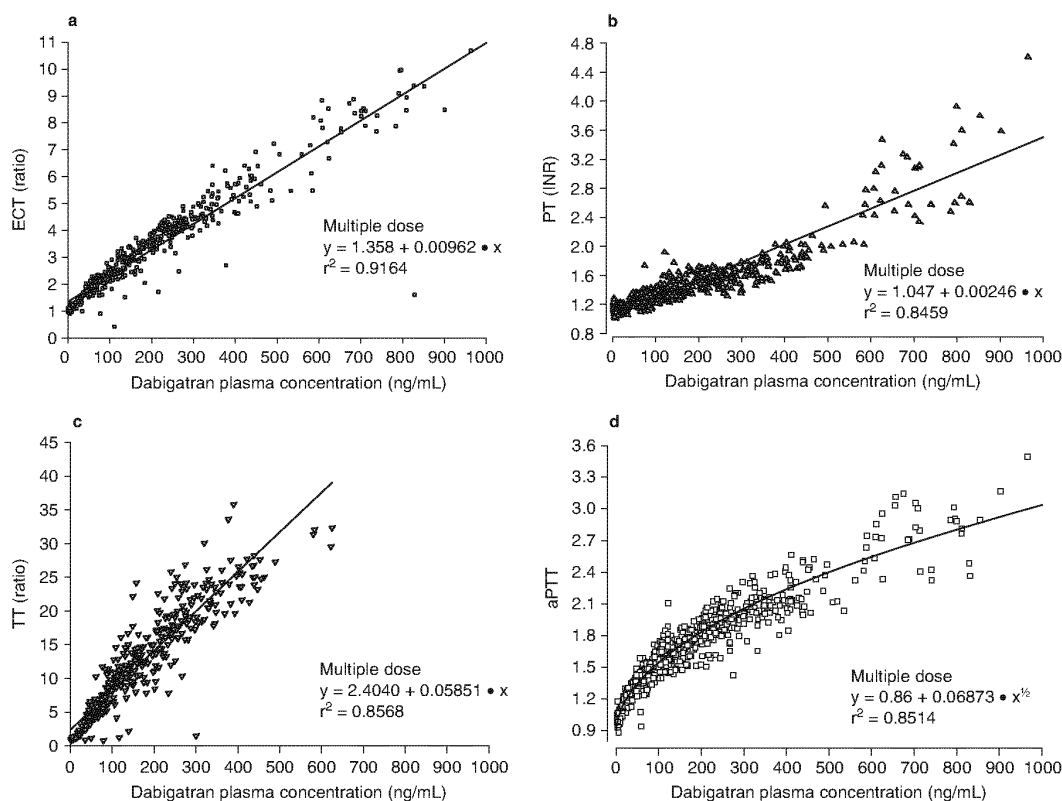


Fig. 2. Prolongation of (a) ecarin clotting time (ECT), (b) prothrombin time (PT) [international normalized ratio (INR)], (c) thrombin clotting time (TT) and (d) activated partial thromboplastin time (aPTT) versus dabigatran plasma concentrations at steady state. The TT frequently exceeded the upper limit of the coagulation measurement time of the coagulation analyser of 500 sec.

etexilate is presented as capsules containing multiple pellets approximately 0.8 mm in diameter. The pellets contain a tartaric acid core coated by dabigatran etexilate. Using this approach, an acidic microenvironment is generated, which increases drug dissolution and absorption and renders the extent of absorption of dabigatran etexilate independent of variations in the gastric pH.^[21,22] After oral administration to healthy volunteers, the prodrug dabigatran etexilate was rapidly absorbed and converted via two intermediates, BIBR 951 and BIBR 1087, to the active form, dabigatran.^[23]

Dabigatran etexilate was administered orally at single doses of 10–400 mg or multiple doses of 50–400 mg three times daily for 6 days. Dabigatran peak plasma concentrations ($C_{\max}$) were reached within 2 hours of administering the prodrug, indicating rapid absorption and conversion to active dabigatran.^[24] The prodrug and its intermediates were hardly detectable in the plasma of healthy subjects, and their areas under the plasma concentration-time curves (AUCs), relative to the AUC of dabigatran in plasma, were below 0.4%.^[25]

After the $C_{\max}$ was attained, dabigatran plasma concentrations declined in a biphasic manner characterized by a rapid distribution phase, resulting in a fall of dabigatran plasma concentrations to <30% of the $C_{\max}$ within 4–6 hours of dosing. Rapid distribution was followed by prolonged elimination, with the terminal half-life ($t_{1/2}$) of dabigatran being 12–17 hours^[24] (figure 3).^[23]

The pharmacokinetic profile of a single dose of dabigatran etexilate predicted the steady-state pharmacokinetic profile of dabigatran;^[24] no time-dependent changes were observed in the pharmacokinetic profile of dabigatran after multiple dosing. The apparent volume of distribution, dabigatran plasma clearance and $t_{1/2}$ were independent of the dose. Residual trough plasma concentrations were present at the end of the 8-hour dose interval when administered three times daily. Dabigatran trough plasma concentrations increased dose-proportionally. Stable trough plasma con-

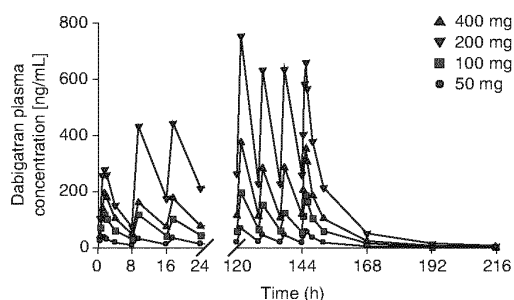


Fig. 3. Geometric mean plot of dabigatran plasma concentration versus time following oral administration of dabigatran etexilate solution 50, 100, 200 or 400 mg three times daily for 6 days and a single dose on day 7 ($n = 8$ subjects per dose group).^[23]

centrations, which indicated that steady state was reached, were attained after 2–3 days of administration. There was no unexpected accumulation of dabigatran over the 6-day treatment period. Interindividual variability of dabigatran steady-state pharmacokinetics in healthy volunteers was low to moderate, with an average interindividual coefficient of variation (CV) of approximately 30%.^[23]

Plasma concentration-time profiles were similar in both young and older volunteers. The pharmacokinetic profiles of dabigatran following multiple doses of dabigatran etexilate 150 mg twice daily for 6 days and a single morning dose on day 7 were examined in elderly (65–87 years) male and female volunteers.^[26] Dabigatran etexilate was rapidly absorbed, with the $C_{\max}$ of dabigatran being attained after 3 hours. After steady state was achieved on day 3, trough plasma concentrations were very stable and displayed low intra- and interindividual variability. The mean steady-state trough plasma concentration with twice-daily administration of dabigatran etexilate 150 mg was 78 ng/mL. Dabigatran plasma concentration-time profiles over a 12-hour dosage interval were obtained on days 4 and 7 of treatment by frequent serial dabigatran concentration measurements. The low CVs of <28% and <15% for inter- and intraindividual variability, respectively, indicated that dabigatran has very predictable pharmacokinetics in older subjects. The AUC of dabigatran was 20–30% higher in elderly females than in elderly males (table I), which was explained by gender-dependent differences in creatinine clearance (CL_{CR}). Compared with healthy young subjects receiving equivalent dabigatran etexilate doses, plasma concentrations in older volunteers were 1.7- to 2-fold higher. Again, this can be rationalized by the decline in kidney function because dabigatran is mainly renally eliminated. The renal clearance of dabigatran ranged between 50 and 100 mL/min.^[22]

The pharmacokinetic profile of dabigatran in patients receiving oral dabigatran etexilate early after orthopaedic surgery was evaluated in a safety study in patients following hip and knee replacement surgery, by means of population pharmacokinetic analysis. Bodyweight, gender, smoking and ethanol consumption were not shown to influence the pharmacokinetics of dabigatran significantly. As expected, on the basis of urinary unaltered drug recovery data obtained in previous studies, CL_{CR} significantly affected drug exposure. The covariate model predicted an increase in drug exposure of 11% for each 10-mL/min decrease in CL_{CR} .^[28,29] This prediction was very similar to that reported for ximelagatran, which was also eliminated by renal excretion in patients with acute DVT.^[30]

The impact of varying CL_{CR} on dabigatran exposure in patients with CL_{CR} of >90, 60–90, 40–60 and <40 L/min was investigated by simulations employing the population pharmacokinetic model

Table I. Pharmacokinetic parameters of dabigatran normalized to a dabigatran etexilate dose of 1 mg in young healthy subjects, elderly subjects and patients after hip and knee replacement surgery^{[21,24,26,27]a}

Parameter	Healthy adult subjects			Healthy elderly subjects		Patients	
	od	bid	tid	bid, male	bid, female	od	bid
C _{max} (ng/mL)/mg	0.89					0.41 ^b	
C _{max,ss} (ng/mL)/mg		1.16	1.68	1.48	1.83		1.06
AUC _∞ (ng • h/mL)/mg	5.66					6.41 ^b	
AUC _{ss} (ng • h/mL)/mg		7.44	7.85	10.9	12.8		15.9
t _{max} (h)	1.25–1.5 ^c					6.0 ^{b,d}	
t _{max,ss} (h)		1.25–2.0 ^c		3.0 ^d	2.5 ^d		2.7 ^d
t _{1/2} (h)	8.13 ^d	11.3 ^d	13.7	12.1 ^d	13.4 ^d		
CL/F (mL/min)	2410	2828	1748	1150	981	1181 ^e	1770 ^e
C _{min,ss} (ng/mL)/mg		0.36	0.50	0.52	0.52	0.13	0.45
C _{max} (fasted/fed) [ng/mL]/mg ^f	0.74/0.71						
AUC _∞ (fasted/fed) [ng • h/mL]/mg ^f	6.03/5.97						
AUC (–P/+P) [ng • h/mL]/mg ^g	6.03/4.70			10.9/8.27	12.8/10.6		

a Values are expressed as mean unless specified otherwise.

b First oral dose after surgery.

c Range.

d Median.

e >24 hours after surgery. Typical values of CL/F for a patient with gastrin of 34.58 pmol/L and CL_{CR} of 76.16 mL/min (Troconiz et al.^[28]).

f Without/with administration of a high-fat, high-calorie breakfast.

g Without/with concomitant administration of pantoprazole (P).

AUC = area under the plasma concentration-time curve; **AUC_∞** = AUC from time zero to infinity; **AUC_{ss}** = AUC at steady state; **bid** = twice daily; **CL_{CR}** = creatinine clearance; **CL/F** = apparent total oral clearance; **C_{max}** = peak plasma concentration; **C_{max,ss}** = peak plasma concentration at steady state; **C_{min,ss}** = minimum plasma concentration at steady state; **od** = once daily; **t_{1/2}** = terminal half-life; **tid** = three times daily; **t_{max}** = time to reach the C_{max}; **t_{max,ss}** = time to reach the C_{max,ss}.

developed for dabigatran in orthopaedic surgery patients.^[28] Simulations were performed assuming a steady-state dosage of 150 mg dabigatran etexilate administered twice daily. The dabigatran C_{max} at steady state (C_{max,ss}) was approximately 100 ng/mL in patients with CL_{CR} of >90 mL/min and 140, 180 and 240 ng/mL in patients with CL_{CR} of 60–90, 40–60 and <40 mL/min, respectively.^[28]

A simulation model developed in hip-replacement surgery patients^[31] was used to simulate the ECT and aPTT values at steady state from 300 subjects with varying degrees of renal impairment at a dabigatran etexilate dosage level of 150 mg twice daily. The simulated subjects were grouped into the following renal function groups: normal renal function (CL_{CR} >80 mL/min), mild renal impairment (CL_{CR} 51–80 mL/min), moderate renal impairment (CL_{CR} 31–50 mL/min) and severe renal impairment (CL_{CR} 10–30 mL/min).

The mean values for the ECT and aPTT response variables increased with decreasing renal function. The increase in bleeding

times was larger when coagulation was measured with the ECT than when coagulation was measured with the aPTT (table II).^[31]

Table II. Simulated dabigatran plasma concentrations and their effect on the blood coagulation parameters activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) in orthopaedic surgery patients with varying degrees of renal impairment based on creatinine clearance after administration of dabigatran etexilate 150 mg twice daily^[28,31]

Renal function	C _{max} (ng/mL)	Ratio ^a	Maximum ECT (s)	Ratio ^a	Maximum aPTT (s)	Ratio ^a
Normal	100		55.2		47.4	
Mild impairment	140	1.4	77.4	1.40	54.2	1.14
Moderate impairment	180	1.8	108	1.95	61.9	1.31
Severe impairment	240	2.4	183	3.32	78.3	1.65

a Ratio of impaired : normal renal function.

C_{max} = peak plasma concentration.

Despite the statistically significant effect of CLCR on dabigatran plasma clearance, the results of simulation studies showed a significant degree of overlap in the drug concentration-time profiles of patients with normal renal function and patients with mild, moderate and severe renal impairment.^[28] This suggested that a fixed-dose regimen of dabigatran etexilate should be used in clinical trials. However, the phase III safety and efficacy clinical trials in the prevention of VTE after elective hip and knee replacement excluded patients with severe renal impairment.

2.1 Oral Bioavailability of Dabigatran Etexilate

Dabigatran is not absorbed after oral administration, because of its high lipophilicity.^[16] Oral administration of the prodrug dabigatran etexilate increases bioavailability. Data on the amount of dabigatran etexilate absorbed are not yet available, although the absolute bioavailability of dabigatran has been reported to be 7%.^[32] The low absolute bioavailability necessitates the use of comparably high doses of the prodrug in phase III clinical trials. In the prevention study programme, doses of 150 and 220 mg were administered once daily.

Low absolute bioavailability could result in nonproportional and highly variable increases in drug plasma concentrations. First-pass elimination is a frequent cause of low drug bioavailability, with the potential for nonproportional increases in drug plasma concentrations and high variability if saturation of the first-pass elimination process occurs. The dose-proportional increase in the dabigatran C_{max} and AUC indicated linear pharmacokinetics of dabigatran over a wide range of doses (10–1200 mg total daily dose) and demonstrates that the pharmacokinetics of dabigatran are predictable despite the low absolute bioavailability. Saturable first-pass elimination of dabigatran can be excluded even at a daily total dose of 1200 mg,^[24] which is 4-fold higher than the maximum clinical daily dose of dabigatran etexilate 300 mg employed in the acute VTE treatment trial RE-COVER (150 mg twice daily) [figure 4].

2.1.1 Effect of Food and Pantoprazole

The effect of a high-fat, high-calorie breakfast on the rate and extent of absorption of dabigatran etexilate, when administered as a single 150-mg dose after breakfast, was studied in two studies in 12 and 18 healthy male volunteers.^[33,34] In the fasted state, dabigatran was rapidly absorbed and reached the C_{max} after 2 hours. Food delayed the time to the C_{max} (t_{max}) of dabigatran by a further 2 hours ($n = 12$; figure 5). Although dabigatran etexilate has low oral bioavailability, the total AUC and C_{max} in both studies remained essentially unchanged under fasted and fed conditions. The mean AUC values in 18 subjects under fasted and fed conditions were 904 and 895 ng • h/mL, respectively, and the C_{max}

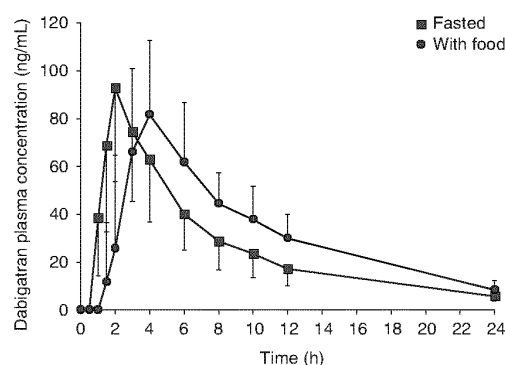


Fig. 5. Mean ($\pm$ SD) plasma concentration-time profiles of dabigatran after single-dose administration of dabigatran etexilate 150 mg capsules to healthy male volunteers in the fasted and fed states.^[34]

values were 111 and 106 ng/mL, respectively. Concomitant food decreased the CV of dabigatran C_{max} from 42% to 24% and the CV of the AUC from 44% to 21%.^[33]

Coadministration of the proton pump inhibitor pantoprazole reduced the average AUC and C_{max} of dabigatran by 22% (904 vs 705 ng • h/mL) and 33% (111 vs 74.5 ng/mL), respectively.^[33] Analysis of the AUC at steady state (AUC_{ss}) in elderly male and female subjects over one dosing interval ($AUC_{\tau,ss}$) showed that the bioavailability of dabigatran with concomitant pantoprazole on

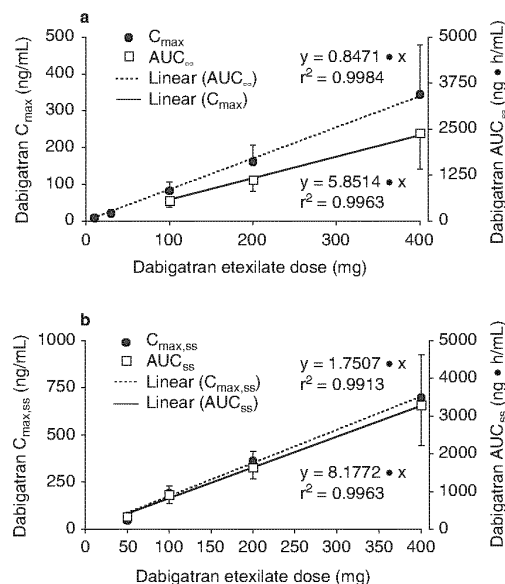


Fig. 4. Dose-proportional increases (mean $\pm$ SD) of (a) the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}), and (b) the C_{max} at steady state ($C_{max,ss}$) and the AUC at steady state (AUC_{ss}) of dabigatran after single- and multiple-dose administration of dabigatran etexilate, respectively.^[24]

day 4 and day 7 of 150 mg twice-daily treatment was 75.9% and 79.6% of the bioavailability without pantoprazole. The $C_{\max,ss}$ values on days 4 and 7 with pantoprazole coadministration were approximately 72% and 75.9% of the $C_{\max,ss}$ without pantoprazole.^[22] Due to the flat dose-response curve of dabigatran, this reduction in the dabigatran plasma concentration was not considered clinically relevant at the target clinical doses of dabigatran etxilate 150 and 220 mg.^[33,35]

2.1.2 Absorption Profile in Patients

The rate and extent of absorption of dabigatran etxilate was investigated in a pharmacokinetic study in patients undergoing elective hip arthroplasty.^[21] The intended commercial capsule formulation of dabigatran etxilate 150 mg was administered to 59 patients within 1–3 hours of completing the surgical procedures. Plasma concentrations of dabigatran were detectable early after oral drug administration, which indicated an immediate onset of absorption of dabigatran etxilate. In two of the 59 patients, absorption of dabigatran etxilate was delayed by 4 and 6 hours following drug administration. The median $t_{\max}$ was 6 hours compared with about 2 hours in young healthy subjects, indicating that dabigatran is absorbed slowly during the early postoperative period. The mean $C_{\max}$ (75.8 ng/mL; 90% CI 65.1, 86.6) was lower than in healthy subjects (111 ng/mL; 90% CI 92.4, 131). Coadministration of opioids had no effect on dabigatran etxilate absorption.^[21] The mean dabigatran AUC of 904 ng • h/mL (90% CI 743, 1060) in this setting was comparable to the AUC seen in healthy volunteers, and amounted to 88% of the AUC seen in patients at steady state (BISTRO I [Boehringer Ingelheim Study in Thrombosis Oral Only]).^[21,29] The interindividual variability of dabigatran pharmacokinetics in patients receiving dabigatran etxilate early after surgery was higher than in healthy subjects. The interindividual CVs for AUC and $C_{\max}$ were 69% and 65%, respectively.^[21,27] In summary, early postoperative oral administration of dabigatran etxilate delayed the $t_{\max}$ and reduced the $C_{\max}$ but had no negative impact on the total exposure (AUC) of dabigatran.

The pharmacokinetic profile of dabigatran after early oral administration of the prodrug to 286 patients was studied by population pharmacokinetic analysis.^[29] In this initial safety study in orthopaedic patients, dabigatran etxilate was administered as a preliminary tablet formulation once daily at doses of 150 and 300 mg, or in the dosage range of 12.5–300 mg twice daily. The first dose was administered within 4–8 hours of surgery. The pharmacokinetics of dabigatran were best described by a two-compartment model with first-order absorption and first-order elimination. Inclusion of a lag time (estimated to be 0.4 hours) was also required. The main characteristic of the population model was

that the rate constant of drug absorption and the apparent plasma clearance during the day of surgery and day 1 of treatment were significantly lower compared with days 2–10 of treatment.^[29] This could be because absorption might be slower directly after surgery because of changes in gastrointestinal motility.^[28] These findings confirm the study results obtained by conventional pharmacokinetic analysis in orthopaedic surgery patients, as discussed earlier (BISTRO Ib).^[21]

In conclusion, dabigatran etxilate was adequately absorbed after early postoperative oral administration. There was no delay in the onset of drug absorption in essentially all patients, leading to therapeutic drug concentrations early after dosing. The pharmacokinetic profile of dabigatran in this setting was characterized by slow and prolonged absorption of dabigatran etxilate. The absence of a high $C_{\max}$ in conjunction with the unchanged dabigatran total exposure (AUC) might reduce the risk of bleeding with early postoperative anticoagulant administration.

2.2 Metabolism and Excretion of Dabigatran Etxilate

Dabigatran etxilate and dabigatran are not metabolized by CYPs to any significant extent. Additionally, dabigatran does not inhibit or induce CYPs activity.^[32] The potential for interactions between dabigatran and drugs metabolized by CYP isoenzymes was therefore considered to be low. *In vitro* studies in human liver microsomes revealed that the conversion of the prodrug dabigatran etxilate to the intermediate BIBR 1087 and to dabigatran is catalysed by microsomal carboxylesterases.^[32] In contrast to the negligible role of oxidative phase I metabolism, about 20% of dabigatran is conjugated by glucuronosyltransferases to pharmacologically active glucuronide conjugates. The glucuronide conjugates are pharmacologically fully active; therefore, glucuronidation has no effect on the clinical efficacy of dabigatran.

Almost complete recovery of radioactivity was observed after oral administration of [^{14} C]-dabigatran etxilate and intravenous infusion of [^{14} C]-dabigatran.^[32] After intravenous infusion, 85% of the dabigatran dose was recovered in urine. Renal clearance (89 mL/min) of dabigatran accounts for about 80% of the total clearance (112 mL/min) following intravenous infusion of dabigatran. The urinary recovery of radioactivity after oral administration amounted to 7.2% of the dose. Primarily, unchanged dabigatran and small amounts of dabigatran glucuronides were recovered in the urine. The volume of distribution of dabigatran administered by intravenous infusion was 50–70 L, indicating moderate tissue distribution of dabigatran.

As determined by population pharmacokinetic analysis in orthopaedic surgery patients, typical estimates of the apparent volumes of distribution of the central and peripheral compartments

were 30.8 L (standard error [SE] 17%) and 136 L (SE 42%), respectively. Covariate analyses did not reveal any effects of covariates such as bodyweight, gender and clinical laboratory measurements on the apparent volumes of distribution.^[32]

Protein binding studies with radiolabelled dabigatran showed that 35% of the dabigatran is bound to plasma proteins.^[32] Because of the low percentage of protein binding, displacement interactions appear to be unlikely and would not affect the pharmacokinetics and pharmacodynamics of dabigatran.

2.3 Hepatic Impairment

The influence of hepatic impairment on the absorption and bioconversion of dabigatran etexilate to the active form dabigatran, and its elimination, were assessed in subjects with moderate hepatic impairment, i.e. Child-Pugh category B.^[25] Healthy control subjects were matched by age, bodyweight and gender. Following a single dose of dabigatran etexilate 150 mg, the mean AUCs in both study groups were comparable. The bioconversion of the prodrug to dabigatran via the intermediate BIBR 1087 was slightly slower in the hepatically impaired group than in the healthy comparator group, but still rapid, with low and transient concentrations of the prodrug and its intermediates being detectable in plasma. The AUCs of dabigatran etexilate and the intermediates BIBR 1087 and BIBR 951 relative to the dabigatran AUC were 1.8%, 5.9% and 0.3%, respectively. In the healthy control group, the low concentrations of the prodrug and its intermediates were difficult to quantify and amounted to <0.4% of the dabigatran AUC. Protein binding and the extent of glucuronidation of dabigatran remained essentially unchanged in subjects with moderate hepatic impairment.^[25]

3. Drug Interaction Studies

Three *in vivo* drug interaction studies with dabigatran etexilate and the following substrates and/or inhibitors of the main metabolic enzymes and drug transporters were reported: (i) the HMG-CoA reductase inhibitor atorvastatin, which is a substrate of CYP3A4 and substrate/inhibitor of the P-glycoprotein (P-gp) efflux transporter; (ii) the NSAID diclofenac, which is a substrate of CYP2C9 and uridine glucuronosyltransferase (UGT) 2B7, and a substrate/weak inhibitor of UGT1A; and (iii) the cardiac glycoside digoxin, which is a model substrate of P-gp. There was no important influence of dabigatran etexilate on the pharmacokinetic/pharmacodynamic effect of atorvastatin and its metabolites 2'-hydroxy-atorvastatin and 4'-hydroxy-atorvastatin, and vice versa.^[36] Co-administration of dabigatran etexilate and digoxin had no relevant effect on the dabigatran pharmacokinetic parameters C_{max} and AUC. $C_{max,ss}$ values of digoxin with and without coadministration

of dabigatran etexilate were bioequivalent, demonstrating no effect of dabigatran etexilate on digoxin pharmacokinetics. This excluded any effect of dabigatran etexilate on the P-gp-mediated transport of digoxin.^[37] The mean AUC_{ss} and $C_{max,ss}$ of dabigatran remained unchanged with a single dose of diclofenac. Effects of diclofenac on the prolongation of blood coagulation by dabigatran, assessed by measurement of aPTT and ECT, were not observed. However, inhibition of blood coagulation, as determined by the bleed time after incision of the forearm skin, was not tested.^[36-38]

4. Pharmacodynamics

The pharmacodynamic profile of dabigatran after oral administration of the prodrug dabigatran etexilate demonstrated effective anticoagulation with a low bleeding risk.^[39-41] The effects of oral dabigatran etexilate on thrombin formation have been reported recently.^[42] Using a thrombin generation test, dabigatran induced a marked lag time and time to peak prolongation, and reduced the mean velocity index of thrombin generation and the amount of active thrombin formed. By the calibrated automated thrombograms used, dabigatran was found to be more active than argatroban.^[43]

Direct thrombin inhibition by dabigatran was measured in healthy young and elderly volunteers, and in post-elective hip or knee replacement surgery patients.^[24,26,44] Different clot-based assays were employed to measure clotting time prolongation by dabigatran. The aPTT assay targets the intrinsic pathway of the coagulation cascade, whereas the PT assay represents the clotting time in the extrinsic coagulation pathway. The thrombin time (TT) and ECT assays directly assess the activity of thrombin and meizothrombin in a plasma sample and provide a direct measure of the activity of DTIs. Time curves for the aPTT (figure 6), PT (expressed as INR), TT and ECT paralleled the dabigatran plasma

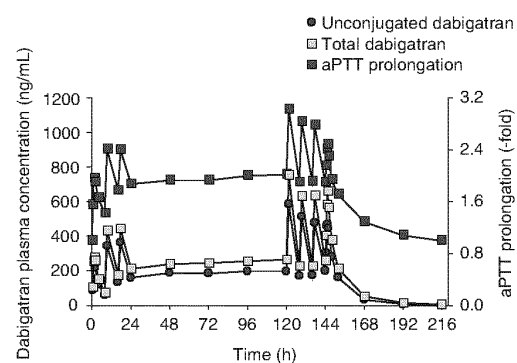


Fig. 6. Geometric mean plasma concentrations of total dabigatran (dabigatran in plasma plus dabigatran glucuronides), unconjugated dabigatran, and activated partial thromboplastin time (aPTT) prolongation (ratio over baseline) after three times daily administration of dabigatran etexilate 400 mg for 6 days.

concentration-time curves, with values increasing rapidly and in a dose-dependent manner, and maximum effects being attained within 2 hours of oral administration.

The maximum effect ($E_{\max}$) of dabigatran on clotting parameters occurred at the same time as the $C_{\max}$, indicating that thrombin inhibition by dabigatran is a direct effect linked to the central plasma compartment. The parallel slopes of blood coagulation prolongation and the corresponding plasma concentration-time curves demonstrated that the pharmacodynamic effects of dabigatran have a rapid onset of action, without a time delay. The offset of action of dabigatran also occurs in parallel with the elimination of dabigatran, such that a rapid initial decrease in the anticoagulant effect was followed by a slow terminal phase. Twelve hours after administration, the prolongation of blood coagulation returned to about 50% of the maximum effect. The slow terminal phase maintained therapeutic concentrations throughout a 24-hour period, whilst retaining sufficient reversibility (figure 4).^[27]

The shallow dabigatran exposure-response curve for efficacy and bleeding shown in the BISTRO II dose-finding study in VTE prevention,^[27,35] in conjunction with the predictable pharmacokinetic/pharmacodynamic relationship of dabigatran, supported the use of a fixed-dose regimen without blood coagulation monitoring.

The pharmacokinetic/pharmacodynamic analyses suggested marked differences between the pharmacodynamic assays in terms of sensitivity and precision at varying dabigatran plasma concentrations. A curvilinear relationship was shown between dabigatran drug plasma concentrations and the aPTT (figure 2), similar to the melagatran/aPTT relationship reported for melagatran.^[13] The flattening of the aPTT-plasma concentration-response curve indicated that this assay was associated with low sensitivity at dabigatran plasma concentrations of >200 ng/mL. Patients with substantially elevated dabigatran levels (>400 ng/mL) almost always have marked prolongations of their aPTT values. Thus, the aPTT may not be suitable for accurately quantifying the anticoagulant effect of dabigatran but provides a qualitative assessment of the anticoagulant activity. At the highest dabigatran etexilate dose administered to healthy male volunteers (400 mg three times daily), 2-fold and 3-fold prolongations in the aPTT at trough and peak were observed. The pharmacodynamic effects of dabigatran declined in parallel with plasma concentrations, with residual effects still present 24 hours after the last administration.^[24]

The data suggest a linear relationship between the plasma concentration and PT; however, this assay^[24] lacked sensitivity within a clinically relevant plasma concentration range.

The TT assay exhibited a linear relationship with plasma concentration, and demonstrated a high level of sensitivity. More than

50-fold prolongations of the TT were reported. The TT might be too sensitive to dabigatran plasma concentrations in the clinically relevant plasma concentration range. At dabigatran concentrations >600 ng/mL, the TT frequently exceeded the maximum measurement time of the coagulometer (figure 2).^[24] The ECT assay displayed a linear relationship with drug plasma concentrations in the clinically relevant drug concentration range, and exhibited adequate sensitivity and precision. Maximum ECT ratios were prolonged 5-fold after a single dose of dabigatran etexilate 200 mg. The prolongations of blood coagulation were very predictable and reproducible. The interindividual CVs of the maximal aPTT prolongation after single and multiple doses of dabigatran etexilate were between 6% and 11%. The moderate variability of dabigatran pharmacokinetics does not translate into variability of the pharmacological response (figure 2).

In BISTRO I, a population pharmacodynamic analysis was performed in order to describe the pharmacokinetic/pharmacodynamic characteristics of dabigatran in patients undergoing elective hip replacement surgery.^[44] The blood coagulation parameters aPTT and ECT were used to assess the pharmacodynamics. The analysis also aimed to investigate the effects of bodyweight, age, gender, CL_{CR} and treatment effects (fed/fasted condition, concomitant medication) on the pharmacodynamic model parameters. Inter- and intraindividual variability in blood coagulation parameters was also studied.

Overall, the prolongation of the aPTT increased in a nonproportional manner with increasing concentrations of dabigatran, as was the case in healthy subjects. A combined $E_{\max}$ model and linear model best described the relationship between dabigatran plasma concentrations and the aPTT at steady state. The pharmacokinetic/pharmacodynamic response was dominated by the nonlinear $E_{\max}$ -type correlation up to a dabigatran plasma concentration of approximately 200 ng/mL, whereas at higher dabigatran concentrations, the pharmacokinetic/pharmacodynamic relationship became linear. The mean (interpatient variability) baseline aPTT was 33.4 seconds (CV 8.7%) and the $E_{\max}$ (the maximum increase in the aPTT contributed by the $E_{\max}$ model) was 26.9 seconds (CV 19.9%). The dabigatran concentration needed to attain 50% of the maximum effect was 94.7 ng/mL (CV 38%), and the mean slope of the linear concentration-response relationship was 0.0509 sec • ng/mL (CV 15.2%). The baseline aPTT and $E_{\max}$ (26.9 seconds) were highest following surgery and declined to 14.4 seconds at infinite time, representing a 46% decrease in the $E_{\max}$.

In contrast to the aPTT model, there was a simple linear relationship between the dabigatran plasma concentration and the prolongation of ECT, again resembling the concentration/ECT relationship in healthy volunteers. However, it was found that the

slope of the line of regression varied with time after surgery, indicating greater sensitivity in the ECT response early after surgery. The slope decreased from 0.38 sec • ng/mL to 0.27 sec • ng/mL, with a $t_{1/2}$ of 1.1 days.^[18]

The greater sensitivity of the blood coagulation parameters aPTT and ECT early after surgery indicated greater pharmacological efficacy of dabigatran etexilate treatment when initiated immediately after surgery. A 50% dose reduction was therefore deemed the most appropriate approach to balance the risk of bleeds with the anticoagulant effect, and therefore this was employed in phase III clinical trials in VTE prevention.

A covariate analysis was performed in order to identify patient or treatment variables that might influence the aPTT and ECT response. The major covariates identified included co-medications (e.g. diuretics, drugs accelerating the gastrointestinal transit time, paracetamol [acetaminophen], CYP3A4 inhibitors), patient demographics and standard clinical laboratory parameters. None of the covariates exhibited relevant effects on any of the aPTT and ECT model parameters.^[44]

5. Conclusion

Effective anticoagulant therapy is crucial for the prophylaxis and treatment of VTE, which is a major cause of morbidity and mortality worldwide. Despite their proven efficacy, the most commonly used anticoagulants, i.e. LMWHs and vitamin K antagonists, are associated with a number of limitations. Dabigatran etexilate, a novel oral DTI, is currently in development to address these limitations. Given its predictable pharmacokinetic profile, fixed oral dosage, low potential for drug-drug interactions and lack of need for coagulation monitoring, dabigatran etexilate can be used in a wide variety of patient populations who require anticoagulation therapy. Dabigatran etexilate shows promise in meeting the current unmet clinical needs in anticoagulation therapy, and has the potential to change the current practice of anticoagulation.

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