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ORIGINAL ARTICLE

Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I

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Summary. *Background:* Dabigatran etexilate (BIBR 1048) is an oral direct thrombin inhibitor undergoing evaluation for the prevention of venous thromboembolism (VTE) following total hip replacement. Following oral administration, dabigatran etexilate is rapidly converted to its active form dabigatran (BIBR 953 ZW). *Objectives:* To determine the safe therapeutic range of dabigatran etexilate following total hip replacement. *Methods:* In a multicenter, open-label, dose-escalating study, 314 patients received oral doses of dabigatran etexilate (12.5, 25, 50, 100, 150, 200 and 300 mg twice daily or 150 and 300 mg once daily) administered 4–8 h after surgery, for 6–10 days. Dose escalation was based on clinical and pharmacokinetic data. The primary safety outcome was major bleeding. The primary efficacy outcome included venographic deep vein thrombosis (DVT), symptomatic DVT and pulmonary embolism, during the treatment period. *Results:* No major bleeding event was observed in any group, but two patients at the highest dose (300 mg twice daily) suffered bleeding from multiple sites associated with reduced renal clearance and prolonged pharmacodynamic (PD) parameters. A dose–response was demonstrated for minor bleeding events. Of the 289 treated patients, 225 patients had evaluable venograms. The overall incidence of DVT was 12.4% (28/225 patients). There was no consistent relationship between the dose and incidence of DVT, the highest incidence in any group being 20.8% (5/24 patients). The lowest dose (12.5 mg twice daily) showed a high rate of proximal DVT [12.5% (3/24)] and no increase in PD parameters. Peak and trough plasma concentrations, area under the dabigatran plasma concentration-time curve and PD parameters also increased in proportion with the dose. Higher dabigatran plasma concentrations were associated with lower DVT rates. Approximately 20% of the patients had low plasma concentrations after the first dose suggesting further optimization of the preliminary tablet formulation is required. *Conclusions:* Dabigatran etexilate demonstrates an acceptable safety profile, with a therapeutic window above 12.5 mg and below 300 mg twice daily. The low number of VTE events within each treatment group indicates a satisfactory antithrombotic potential, although the study was not powered for an efficacy analysis. Additional studies are ongoing to optimize oral absorption and the efficacy/safety balance.

Keywords: dabigatran etexilate, deep vein thrombosis, direct thrombin inhibitor, total hip replacement.

Introduction

Dabigatran (BIBR 953 ZW) is a low-molecular-weight direct thrombin inhibitor (DTI) that binds to thrombin with a high affinity and specificity and which can be administered orally as the prodrug dabigatran etexilate (BIBR 1048). It is undergoing evaluation for the prevention of venous thromboembolism (VTE) following major lower limb orthopedic surgery.

In preclinical studies dabigatran has shown excellent potential as an antithrombotic agent [1,2]. In studies of healthy male volunteers dabigatran etexilate was well tolerated with no evidence of major bleeding at doses from 10 to 400 mg when given up to three times daily for 7 days

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[3,4]. Bruising at venipuncture sites and gum bleeding did occur at a dose of 400 mg three times daily. The pharmacokinetic profile (PK) of dabigatran in healthy volunteers, using a solution formulation of dabigatran etexilate, showed peak plasma concentrations within 2 h, a bi-exponential distribution phase and a terminal half-life of 14–17 h after multiple dosing [3]. Maximal plasma concentrations and area under the plasma concentration–time curve all increase in a dose-proportional manner. Accumulation of dabigatran is demonstrated with twice and thrice daily dosing with steady state conditions being attained by 2–3 days with twice daily administration. A close correlation exists between dabigatran plasma concentrations and pharmacodynamic (PD) effect; persistent prolongation of activated partial thromboplastin time (aPTT) being observed at the end of 8- and 12-h dosing intervals.

Current guidelines for development of new anticoagulant drugs recommend evaluation in a setting of high thromboembolic risk [5]. Elective total hip replacement (THR) is one type of surgery in which historically more than 50% of the patients develop deep-vein thrombosis (DVT) in the absence of thromboprophylaxis [6]. Furthermore, patients undergoing elective THR represent a relatively stable and homogeneous population that has become a benchmark for the development of new anticoagulant therapies. Good insights into the efficacy and safety of compounds are provided with the use of small numbers of patients [5]. This ascending dose ranging study was designed to investigate the therapeutic window of dabigatran etexilate to select doses for further development of the compound.

Patients and methods

Patients

Consecutive patients were considered for inclusion if they were aged over 18 years, weighed at least 40 kg and were scheduled for primary elective THR. Patients were excluded if they had: any bleeding diathesis; constitutional or acquired coagulation disorders; undergone major surgery or trauma (e.g. hip fracture) within the last 3 months; had a cardiovascular disease including uncontrolled hypertension at the time of enrollment or history of myocardial infarction within the last 6 months; any history of hemorrhagic stroke; intracranial or intraocular bleeding or cerebral ischemic attacks; known history of DVT; gastrointestinal or pulmonary bleeding within the last year; known liver disease; known renal disease (serum creatinine $>$ 1.5 $\times$ upper limit of normal); use of long-term anticoagulants, antiplatelet drugs, or fibrinolytics within 7 days prior to THR (also contraindicated during the period of prophylaxis); known allergy to radiopaque contrast media; known thrombocytopenia; active malignant disease; current H_2 blocker or proton pump inhibitor treatment; current cytostatic treatment or treatment with an investigational drug in the past month. Also excluded were those with leg amputations, known alcohol or drug abuse and women of childbearing potential.

Study design

This was a multicenter, open label, sequential dose escalating study conducted at 11 sites in Sweden and seven in Norway. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by National Independent Ethics Committees and written informed consent was obtained from all patients prior to inclusion.

Dabigatran etexilate was administered using a tablet formulation in doses of 12.5, 25, 50, 100, 150, 200 and 300 mg twice daily, or 150 and 300 mg once daily. This dose range was determined on the basis of previous studies in healthy volunteers [3]. Patients received the first dose of dabigatran etexilate 4–8 h after completion of surgery. The next dose was given on the following day at approximately 08.00 h, resulting in a dosing interval of at least 12–16 h. If the patient vomited or had bleeding problems after surgery the first dose of dabigatran etexilate could be postponed until the next morning. Treatment was continued for 6–10 days. During treatment, long-acting non-steroidal anti-inflammatory drugs with a half-life of 12 h or more and mechanical prophylaxis (intermittent pneumatic compression devices) were not allowed although elastic compression stockings were permitted. Antacids could be used, however, administration was limited to 2 h prior to or following study drug administration. On the last day of dabigatran etexilate administration, mandatory bilateral venography was performed. Continued anticoagulation after this time period was at the discretion of the investigator. Patients were assessed at a follow-up visit 4–6 weeks after surgery.

Escalating doses depended on the safety data, principally bleeding information and occurrence of thromboembolic events at particular dose levels. The decision to continue testing at that dose, increase to a higher dose, or stop dosing was made by the Steering Committee in conjunction with predefined guidelines. Safety was evaluated by examining blood loss volume, transfusion requirements and clinical bleeding events. Local assessment of DVT, measured by venography, was used since rapid ongoing evaluations of venograms were required for decision making in this sequential study. All patients in a given dose group received only that dose of study medication. All patients initially entered into the study received the lowest dose of dabigatran etexilate (12.5 mg twice daily). It was planned that a once daily dosing would be tested in at least one dose group approximating the maximal tolerable dose. This ascending dose procedure was continued until patients had been entered into 9 different groups from 12.5 mg to 300 mg, twice daily.

Safety assessments

The primary safety outcome was the rate of major bleeding events during the treatment phase (bleeding episodes before the first dose of dabigatran etexilate were excluded). Major

bleeding was defined according to recommended guidelines [5,7] and included clinically overt bleeding associated with ≥ 20 g L^{-1} fall in hemoglobin, clinically overt bleeding leading to transfusion of ≥ 2 units packed cells, retroperitoneal, intracranial, intraocular or intraspinal bleeding. During the study investigators were reminded that overt bleeding should only include bleeding at the surgical site that was considered excessive or unexpected according to their usual practice. Minor bleeding included any other manifestation of bleeding no matter how small. If major bleeding occurred, further enrollment and treatment could be halted due to unacceptable safety, as judged by the Steering Committee, or a once daily regimen implemented. All bleeding events (major plus minor) were evaluated according to increasing dose. Furthermore, laboratory parameters were assessed which may be indicative of an increased bleeding risk. Adverse events reported by patients, as well as those observed or detected by the investigator, were recorded throughout the study. Adverse events were classified according to the WHO adverse event dictionary. An independent expert classified all bleeding events.

Efficacy assessments

The primary efficacy outcome was the rate of VTE events in each group. VTE included DVT detected by venography, symptomatic and objectively confirmed DVT and PE. Bilateral venography was performed according to a modified technique of Rabinov and Paulin [8–10]. This required venography to be performed in a semi-upright position (preferably 60° elevation from the horizontal plane), using adequate volumes of contrast media (preferably 100 mL per leg), and without the use of lower limb tourniquets. A central panel of two experts adjudicated all venograms. The venograms were judged adequate for evaluation if they bilaterally demonstrated complete visualization of all deep veins or if a DVT was found. DVT was diagnosed when a constant intraluminal filling-defect was seen on at least two images. Proximal DVT was defined as DVT in or above the popliteal vein. The secondary efficacy outcome was objectively confirmed VTE during the follow-up period.

Two PD parameters were also considered as primary outcomes. The aPTT and ecarin clotting time (ECT) were determined by centralized clinical laboratory assay of blood samples drawn at various times during treatment.

Drug concentration and pharmacokinetic assessments

Monitoring of dabigatran plasma concentration was performed on all patients to assess drug exposure and to determine the PK profile of dabigatran in patients receiving dabigatran etexilate. Dabigatran plasma concentrations were measured 4 h after the first dose, before subsequent doses (trough), and 2 h after drug administration. On day 4 or 5 serial PK sampling was performed prior to dosing and then 2–4, 4–8, and 8–12 h post dosing. These measures were analyzed in conjunction with the PD measures. A steady state profile of plasma concentration vs. time for dabigatran following drug administration was obtained for each patient who had taken the morning dose on days 4 or 5. From the dabigatran plasma concentration–time profile the extent of absorption of dabigatran at steady state (AUC_{ss}) was calculated and in addition, the maximal plasma concentrations ($C_{max,ss}$) were determined.

Statistical analyses and monitoring guidelines

All statistical analyses were conducted according to the treatment given. As the dose-limiting factor was expected to be major bleeding events, guidelines were formulated to identify an excessive incidence of major bleeding events. Administration of the current dose was to be stopped if two major bleeding events occurred in $\leq$ six treated patients, or three in ≤ 15, or four in ≤ 25, or five in ≤ 30. Any of these outcomes would be inconsistent with an acceptable major bleeding rate $\leq 5\%$. No further treatment with the current or higher dose regimen was allowed without unanimous agreement by the Steering Committee.

Although the study was not powered to detect differences in efficacy, it was planned that if a dose group had 25 patients evaluable for VTE, comparisons with published historical rates with no anticoagulation (50%) and LMWH VTE prophylaxis (15–17%) would be made [1]. Based on consideration of the confidence intervals, this translated to fewer than or equal to eight patients with VTE among 25 evaluable patients, resulting in the conclusion that a specific dose of dabigatran was more effective than no VTE prophylaxis and not significantly worse than the expected outcome with LMWH prophylaxis.

After a regimen had shown an acceptable safety profile in ≥ 10 patients, the Steering Committee could also terminate enrollment due to unacceptable efficacy failure before evaluating 25 patients. Enrollment at the current dose could be stopped and commenced at the next higher dose if $\geq$ five patients developed VTE in ≤ 10 evaluable patients or nine patients had VTE in ≤ 25. Either outcome would indicate an unacceptable VTE rate of $> 20\%$.

Continuous monitoring of locally diagnosed VTE, major bleeding events and serious adverse events was employed by the Steering Committee to reveal unacceptable safety or efficacy before the full complement of 25 evaluable patients had been observed. The Committee was closely guided by, but not restricted to, the above guidelines. Although local evaluations were sufficient for efficacy monitoring during the study, blinded, centralized venogram reading was used in the final efficacy analysis.

The number of patients with VTE and bleeding parameters was evaluated in each dose group along with the discrete 95% confidence intervals for the VTE rate at each dose. Logistic regression analyses of safety and efficacy outcomes and PK/PD parameters for dabigatran were performed.

Results

Patients

The study enrolled 314 patients between October 2000 and June 2001 with 289 receiving at least one dose of dabigatran etexilate. Twenty-seven patients discontinued treatment early; 18 due to an adverse event. Two hundred and sixty-two patients (90.7%) completed the study. The safety population consisted of all 289 treated patients. The efficacy population consisted of the 225 treated patients with evaluable or otherwise positive venograms.

Patient demographic and surgical characteristics were similar for all treatment groups (Table 1). The mean age was 67 years (range 35–88 years), and 53% of patients were female. The main reason for surgery was osteoarthrosis (93% of patients) and anesthesia was predominantly regional (86%). No significant differences occurred between treatment groups for other medical and surgical variables. The median time interval between surgery and first dose of dabigatran etexilate was 4.9 h (range 1.4–22 h). In one center patients did not receive their first dose until 16–22 h after surgery, accounting for 77% of all patients with postponed administration. Median treatment duration, defined as days on which treatment occurred, was 8 days (range 1–11 days). Two patients were lost to follow-up at 4–6 weeks.

Safety results

A total of 289 patients were treated across the nine dose levels. Blood loss both before and during treatment with dabigatran etexilate was carefully monitored. Most blood loss occurred during surgery or prior to administration of dabigatran etexilate. A weak dose–response relationship was seen for the incidence of bleeding events requiring blood transfusion (Table 2). On average, 7% of treated patients had a bleeding event requiring blood transfusion. All occurred among the six highest doses, with none among the three lowest doses. No dose-related increase of the incidence or volume of transfusions was observed on treatment. A strong dose–response relationship occurred between minor bleeding events and increasing dose of dabigatran etexilate.

Although no patients developed a major bleeding event according to the predefined criteria, the study was discontinued at the 300 mg twice daily dose level when two of the 20 patients experienced bleeding episodes from multiple sites within a few days of treatment. These patients, however, had trough plasma concentrations three- to fivefold higher (535 and 823 ng mL^{-1}) than the geometric mean concentrations for that treatment group, along with substantial prolongation in their aPTT and ECT. Both patients also had low calculated creatinine clearances (43 and 45 mL min^{-1}). A further two patients receiving this same dose showed high trough plasma concentrations (345 and 583 ng mL^{-1}), associated with prolonged aPTT and ECT although they did not experience any bleeding episodes.

Efficacy results

The frequency of DVT events for different doses is shown in Table 3. The overall DVT rate was 12.4% (28/225 patients). Patients receiving the 12.5 mg twice daily dose showed the highest total and proximal DVT rates (20.8% and 12.5%, respectively). The lowest total DVT rates occurred at the higher 300 mg once and twice daily doses (6.1 and 0%). No consistent dose–response relationship was observed. No patients developed symptomatic DVT during the treatment period, while

Table 1 Baseline characteristics of all treated patients

	Dose of dabigatran etexilate (mg)									
Characteristic	12.5 bid	25 bid	50 bid	100 bid	150 qd	150 bid	200 bid	300 qd	300 bid	All
n	27	28	30	40	41	29	28	46	20	289
Age										
Mean	68	65	67	67	66	67	67	67	70	67
Range	50–88	35–85	52–86	45–80	44–82	49–79	55–82	50–84	47–82	35–88
Weight (kg), mean	78	80	76	80	80	81	76	77	75	78
Female sex										
Number	11	12	17	24	20	12	16	26	14	152
Percentage	40.7	42.9	56.7	60.0	48.8	41.4	57.1	56.5	70.0	52.6
Body mass index* (mean)	26	27	26	28	27	27	26	27	26	27
Characteristics of surgery										
Duration of surgery (h) mean	1.7	1.7	1.8	1.7	1.7	1.6	1.8	1.8	1.9	1.7
Time to first dose (h)†										
Median	5.2	4.9	5.0	4.6	4.7	4.8	5.3	4.7	4.6	4.9
Range	4.0–20.4	2.5–21.3	2.4–21.3	3.7–21.8	3.7–16.3	1.4–21.3	4.0–20.9	3.9–21.1	3.3–15.8	1.4–21.8

bid, twice daily; *n*, number of patients operated and treated; qd, once daily. *Body mass index = kg m^{-2}. †Time from operation to first postoperative dabigatran etexilate administration.

Table 2 Summary of bleeding parameters as a function of dabigatran etexilate

	Dose of dabigatran etexilate (mg)									
	12.5 bid	25 bid	50 bid	100 bid	150 qd	150 bid	200 bid	300 qd	300 bid	All
n	27	28	30	40	41	29	28	46	20	289
Blood loss (mL), median										
During surgery (range)	500 (0–1400)	550 (250–2000)	600 (250–1500)	493 (200–1500)	500 (150–1100)	600 (150–1600)	600 (250–1199)	500 (200–1300)	600 (250–2600)	500 (0–2600)
After surgery to first dose (range)	300 (100–600)	300 (40–700)	255 (70–525)	200 (0–1060)	213 (40–1020)	340 (30–2200)	263 (60–990)	300 (50–1092)	275 (30–1275)	250 (0–2200)
During treatment (range)	240 (20–580)	150 (30–820)	300 (15–1400)	260 (0–1200)	400 (0–1200)	300 (0–1200)	220 (0–1160)	360 (0–1020)	355 (0–2300)	300 (0–2300)
Bleeding events requiring transfusion (%)	0	0	0	4 (10.0%)	1 (2.4%)	5 (17.2%)	2 (7.1%)	5 (10.9%)	2 (10.0%)	19 (6.6%)
Major bleeding events	0	0	0	0	0	0	0	0	0	0
Minor bleeding events (%)	2 (7.4%)	9 (32.1%)	18 (60.0%)	33 (82.5%)	39 (95.1%)	26 (89.7%)	22 (78.6%)	41 (89.1%)	16 (80.0%)	206 (71.3%)

n, number of patients operated and treated; bid, twice daily; qd, once daily.

Table 3 Summary of efficacy and pharmacodynamic outcomes

	Dose of dabigatran etexilate (mg)									
	12.5 bid	25 bid	50 bid	100 bid	150 qd	150 bid	200 bid	300 qd	300 bid	All
Efficacy outcomes										
Evaluable patients	24	21	27	31	33	21	21	33	14	225
Total DVT (%)	5 (20.8%)	2 (9.5%)	4 (14.8%)	6 (19.4%)	3 (9.1%)	2 (9.5%)	4 (19.0%)	2 (6.1%)	0	28 (12.4%)
95% CI	7.1–42.2	1.2–30.4	4.2–33.7	7.5–37.5	1.9–24.3	1.2–30.4	5.4–41.9	0.7–20.2	0–23.2	8.4–17.5
Proximal DVT (%)	3 (12.5%)	1 (4.8%)	1 (3.7%)	2 (6.5%)	0	0	1 (4.8%)	1 (3.0%)	0	9 (4.0%)
95% CI	2.7–32.4	0.12–23.8	0.09–19.0	0.8–21.4	0–10.6	0–16.1	0.12–23.8	0.08–15.8	0–23.2	1.8–7.5
Pharmacodynamic outcomes										
Evaluable patients for aPTT	24	26	28	38	37	27	26	39	16	261
Peak aPTT ratio (mean)	1.08	1.10	1.18	1.37	1.38	1.45	1.73	1.73	1.91	–
Evaluable patients for ECT	27	27	30	38	39	27	26	39	16	269
Peak ECT ratio (mean)	0.96	1.11	1.46	2.04	2.08	2.51	3.42	3.29	5.17	–

aPTT, activated partial thromboplastin time; bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; ECT, ecarin clotting time; qd, once daily.

two patients developed a symptomatic DVT in the follow-up period. No PE events or deaths occurred during either period.

Pharmacokinetic parameters

Following oral administration of dabigatran etexilate, plasma concentration increased rapidly in the majority of patients to high levels after 2 h. This was apparent from trough and 2 h post dose sampling and deduced from the steady state plasma concentration time profile on day 4 or 5. Twice daily administration resulted in accumulation of dabigatran reflected by increased trough plasma concentrations, with steady-state conditions being reached on days 2–3. Less accumulation and lower dabigatran trough concentrations were observed with once daily administration. Both the peak plasma concentration and AUC at steady state increased in a dose proportional manner (Table 4). High interindividual variability of plasma concentrations and AUC were noted with the coefficient of variation usually greater than 60%. The effect of renal function on the elimination of dabigatran was assessed by regression analysis. A clear relationship was demonstrated between increased dabigatran trough concentrations and low creatinine clearance (data not shown). Levels of dabigatran increased with decreasing creatinine clearance, especially when less than 50 mL min^{-1}. Logistic regression analysis showed a trend for a decreased rate of DVT and an increase in overall bleeding with increasing plasma concentration and AUC at steady state (data not shown).

Absorption profile following administration of the first dose

Due to the surgical procedures and administration of comedications with potential effects on drug absorption (e.g. opioid induced gastroparesis), the absorption profile of dabigatran etexilate early after surgery was investigated. Poor or delayed absorption of the first dose, which occurred in 53 (18%) of 289

Table 4 Pharmacokinetic parameters of dabigatran according to dose

	$C_{pre,ss}$ (ng mL^{-1})			$C_{max,ss}$ (ng/mL)			AUC_{ss} (ng·h mL^{-1})		
Dose (mg)	gmean	*N*	gCV%	gmean	*N*	gCV%	gmean	*N*	gCV%
12.5 bid	4.7	27	60	10.0	27	60	74.6	25	54
25 bid	8.0	27	65	18.2	27	78	146	25	71
50 bid	19.1	30	94	42.7	29	88	308	26	88
100 bid	43.7	39	67	104	38	68	787	37	73
150 qd	14.3	39	84	99.2	37	84	1020	36	75
150 bid	68.2	26	68	146	26	79	1080	26	76
200 bid	107	28	65	242	26	84	1880	25	61
300 qd	29.0	40	94	232	38	73	2200	38	69
300 bid	182	16	109	338	15	101	2920	16	115

$C_{pre,ss}$, pre dose steady state plasma concentrations; $C_{max,ss}$, peak plasma concentration at steady state; AUC_{ss}, area under the plasma concentration-time curve at steady state; AUC_{ss} for the bid treatment regimen measured for first 12 h after the morning dose; AUC_{ss} for the q.d. treatment regimen measured for 0–24 h after dose; gmean, geometric mean; gCV%, geometric coefficient of variation (%); *N*, number of subjects; bid, twice daily; qd, once daily.

patients, was deduced from low plasma concentrations measured 4 h after administration. Low trough levels on subsequent days would further indicate poor absorption occurred not only after the first dose but for the whole treatment period. This was however, not observed. Further examination of plasma concentrations obtained by more frequent sampling from 10 patients receiving the 300 mg dose showed that delayed absorption of the first dose resulted in peak plasma concentrations not being reached until 4–6 h after administration. No relationship however, was observed between low dabigatran concentrations on the day of surgery, the dose received or the subsequent development of DVT.

Pharmacodynamic parameters

Using linear regression analysis, a close correlation was seen between the prolongation of blood coagulation parameters (ECT, aPTT) and plasma concentrations of dabigatran. A linear relationship was noted for ECT, while for aPTT, the prolongation with increasing dabigatran concentrations showed a non-linear relationship (data not shown). Maximum prolongations of aPTT and ECT (expressed as ratio) increased with dose. Prolongations of aPTT at the end of the dosing interval (trough aPTT ratio at steady state, Fig. 1) increased in proportion with dose.

Adverse events, laboratory

There was no evidence for dose dependent increase in adverse events (AE) other than bleeding events. A total of 17 patients reported 17 serious AE during the treatment period, five of which were judged attributable to the study drug by investigators. No patients died during the study. The liver enzymes AST and ALT increased during treatment for patients at all dose levels, even for the lowest dose (12.5 mg twice daily), which appeared to exert little or no PD effect. There was no dose–response relationship, with large and small increases appearing sporadically across the nine dose levels. Changes in alkaline phosphatase values were also observed, with no apparent relationship to dose of the study drug.

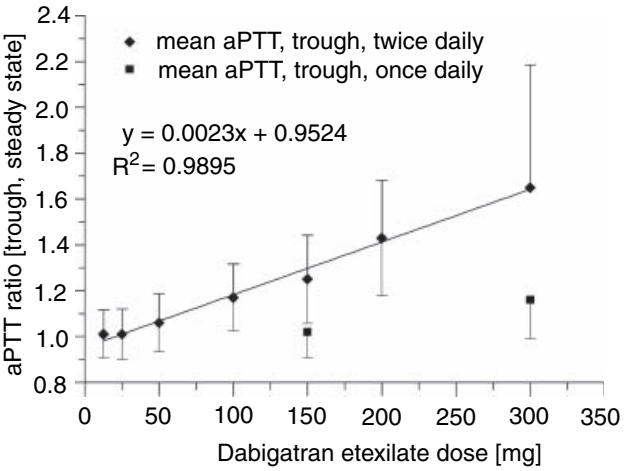

Fig. 1. Mean steady state trough aPTT ratios vs. dose of dabigatran etexilate. aPTT, activated partial thromboplastin time; R^2, coefficient of linear correlation.

Discussion

This study was designed to determine the minimal effective and maximal tolerated doses of dabigatran etexilate for the prevention of thromboembolism in patients undergoing THR. Patients were treated across nine dose levels from 12.5 mg to 300 mg twice daily with dose escalation occurring only when there was sufficient confidence of patient safety. Being the first study of dabigatran etexilate in a patient population, the primary focus was the determination of safety, i.e. the maximal tolerated dose. Only large differences in DVT rates were expected to be detectable due to the limited sample size per dose group.

No major bleeding episodes occurred at any of the doses studied according to the predefined definition. Two patients,

however, experienced bleeding from multiple sites at the 300 mg twice daily dosage. This dose was therefore considered to be at or above the maximum tolerable dose for patients undergoing THR and led to cessation of the dose escalation. Retrospectively, the predefined major bleeding criteria used [5,7], were of limited value in determining the highest tolerable dose. The lack of any major bleeding episodes in a dose escalating study like this is unusual and may be explained by the exclusion of bleeding events during the peri-operative period, prior to the first dose of dabigatran etexilate. Furthermore, investigators were advised to record clinically overt episodes at the surgical site only if they were excessive or unexpected according to their usual practice. All other bleeding events, no matter how small were also counted. This differs from classifications used in other studies, resulting in a potentially higher number of minor bleeding events.

The frequency of minor bleeding episodes (e.g. hematoma, urinary bleeding, nose bleeding, and prolonged bleeding after vein puncture) did increase in a dose-proportional manner suggesting that the drug was in fact exerting its expected pharmacologic dose–response. This was confirmed by measurements of PD parameters (especially ECT) displaying linear increases with increasing plasma concentration of dabigatran. Peak and trough plasma concentrations and the AUC increased dose proportionally, although interindividual variations were high.

Retrospective analyses of the two patients who experienced multiple bleeding events at the 300 mg twice daily dose showed both to have high trough plasma concentrations and low calculated creatinine clearances. A calculated creatinine clearance below 50 mL min^{-1} seems to be a possible contributory explanation for the two bleeding episodes, although the lack of bleeding episodes in another two patients with similar renal function suggests that the elevation in PK and PD parameters may not be the sole reason for the bleeding episodes. Based on predominant renal excretion of dabigatran (80%) and its long plasma half-life (14–17 h), patients with severe renal impairment may have elevated plasma concentrations with twice daily dosing.

The overall DVT rate in this study was low (12.4%), which might indicate a satisfactory antithrombotic potential, although the study was not powered for an analysis of efficacy. The DVT rate is within the range for effective doses of LMWHs and is consistent with other phase IIa dose ranging DTI studies [11,12]. The lowest doses of dabigatran etexilate, 12.5 and 25 mg twice daily, showed minimal effects on prolongation of the coagulation parameters with higher DVT rates. The higher doses (300 mg once or twice a day) showed consistent increases in coagulation parameters with lower DVT rates. Overall, there was a trend for decreased incidence of DVT with increased plasma levels of dabigatran and PD parameters.

Due to the small number of patients evaluated it was not possible to detect any differences in efficacy and safety between once and twice daily dosing of dabigatran etexilate. Available data do not appear to show any disadvantage to once daily dosing compared to twice daily dosing. Bleeding events were essentially identical for the two dosing regimens (150 mg twice daily compared to 300 mg once daily for the 300 mg day^{-1} dose) with only small differences in thromboembolic events.

It is possible that reduced absorption of dabigatran etexilate among some individuals contributed to variability in event rates seen for efficacy and safety outcomes. Nearly one in five patients showed poor or delayed absorption of the first dose administered following surgery. This may have been due to the use of a suboptimal preliminary tablet formulation in the study, which resulted in low solubility of the active ingredient at higher pH. An elevated gastric pH may influence drug absorption, although we attempted to reduce this possibility by excluding patients from the study who were taking H2 antagonists, proton pump inhibitors or antacids. Additionally, absorption may have been impaired by administration of comedications (such as opioids) that affect gastric motility. Finally, absorption of dabigatran etexilate early in the postoperative period may have been delayed due to postoperative intestinal paresis and vomiting. This was demonstrated in a few patients in the highest dose group, in whom more frequent PK samples were taken on the day of surgery. Peak plasma concentrations in these patients occurred 4–6 h following drug administration, compared with a peak at 2 h once steady-state was achieved. On subsequent post operative days, many of these factors have resolved and improved absorption was evident.

Development of a new oral antithrombotic therapy in close proximity to surgery represents a challenging proposition in comparison to existing parenteral therapies. The effect of the postoperative state on drug absorption creates difficulties in achieving an optimal formulation with prompt absorption and significant anticoagulant effect in the majority of patients without compromising safety. Reassuringly, a low incidence of vomiting was noted in the early postoperative period with the majority of patients able to tolerate early administration of fluids.

The therapeutic window for dabigatran etexilate administered orally to patients following THR would appear to start at doses greater than 12.5 mg twice daily. The minimal increase in APTT and ECT and high rate of proximal DVT (12.5%) would suggest that this dose is at or near the 'no effect' dose. Higher doses appeared to exert a therapeutic benefit, but this requires confirmation in larger studies. Besides bleeding which became dose limiting near 300 mg twice daily there did not appear to be any other dose-related increases in adverse events. It is thought unlikely that any increases in liver enzymes were due to treatment with dabigatran etexilate, since the increases were not dose dependent. However, measurements were not taken prior to commencement of dabigatran etexilate treatment, and no control group was studied. Similar increases in liver enzymes are also reported in clinical studies using other anticoagulants such as unfractionated heparin, LMWH and hirudin [13,14].

In summary, this dose finding study shows that dabigatran etexilate demonstrates an acceptable safety profile across a

wide range of doses. The therapeutic window appears to be above 12.5 mg and below 300 mg twice daily. Future studies will focus on optimizing absorption of the dabigatran etexilate oral formulation and timing of the first postoperative dose.

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Addendum

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