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Pharmacokinetics, pharmacodynamics, safety and tolerability of multiple ascending doses of ticagrelor in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The antiplatelet agent clopidogrel is currently the recommended treatment for acute coronary syndrome (ACS).
- Inhibition of platelet aggregation (IPA) with clopidogrel is insufficient, which increases the risk for recurrent ischaemic events. Therefore, there is a need for antiplatelet agents with improved IPA.
- Ticagrelor (AZD6140) is a new antiplatelet agent in clinical development for reduction of thrombotic events in patients with ACS.

WHAT THIS STUDY ADDS

- This study assesses the optimal dosing schedule for ticagrelor in healthy volunteers and compares the degree of IPA with clopidogrel.
- Our findings illustrate that the pharmacokinetics of ticagrelor are predictable and are associated with consistent inhibition of platelet activity.
- IPA with ticagrelor was greater and better sustained at high levels with twice daily ticagrelor than once daily regimens.

AIM

To determine the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple oral doses of ticagrelor, a $P2Y_{12}$ receptor antagonist, in healthy volunteers.

METHODS

This was a randomized, single-blind, placebo-controlled, ascending dose study. Thirty-two subjects received ticagrelor 50–600 mg once daily or 50–300 mg twice daily or placebo for 5 days at three dose levels in two parallel groups. Another group of 16 subjects received a clopidogrel 300 mg loading dose then 75 mg day^{-1}, or placebo for 14 days.

RESULTS

Ticagrelor was absorbed with median t_{max} 1.5–3 h, exhibiting predictable pharmacokinetics over the 50–600 mg dose range. Mean C_{max} and AUC for ticagrelor and its main metabolite, AR-C124910XX, increased approximately dose-proportionately (approximately 2.2- to 2.4-fold with a twofold dose increase) over the dose range. Inhibition of platelet aggregation (IPA) with ticagrelor was greater and better sustained at high levels with ticagrelor twice daily *vs.* once daily regimens. Throughout dosing, more consistent IPA was observed at doses $\geq$300 mg once daily and $\geq$100 mg twice daily compared with clopidogrel. Mean IPA with ticagrelor $\geq$100 mg twice daily was greater and less variable (93–100%, range 65–100%) than with clopidogrel (77%, range 11–100%) at trough concentrations. No safety or tolerability issues were identified.

CONCLUSIONS

Multiple dosing provided predictable pharmacokinetics of ticagrelor and its metabolite over the dose range of 50–600 mg once daily and 50–300 mg twice daily with C_{max} and AUC(0,*t*) increasing approximately dose-proportionally. Greater and more consistent IPA with ticagrelor at doses $\geq$100 mg twice daily and $\geq$300 mg once daily were observed than with clopidogrel. Ticagrelor at doses up to 600 mg day^{-1} was well tolerated.

Introduction

Current standard treatment for acute coronary syndrome (ACS) is clopidogrel in combination with aspirin [1]. Clopidogrel is the only thienopyridine antiplatelet therapy currently recommended by the National Institute for Health and Clinical Excellence (NICE) for the management of non-ST-segment elevation ACS in people at moderate-to-high risk of myocardial infarction or death [2]. However, clopidogrel has been shown to produce an overall low degree of inhibition of platelet aggregation (IPA) and wide response variability (approximately 15–48% of patients have a poor platelet inhibition response to clopidogrel) [3–6]. Furthermore, growing evidence suggests that persistence of enhanced platelet reactivity despite the use of clopidogrel is associated with adverse clinical outcomes, including an increased risk for recurrent ischaemic events [6–11]. Some of the limitations of clopidogrel have been addressed by prasugrel, a recently approved thienopyridine that has demonstrated more consistent platelet inhibition [12]. However, prasugrel was associated with significantly increased risk of major bleeding, including life-threatening and fatal bleeding [12, 13]. There is therefore still a need for new antiplatelet therapies for ACS that provide high and consistent IPA [14–17].

Ticagrelor (AZD6140) is the first reversibly binding oral $P2Y_{12}$ receptor antagonist, which is in clinical development for the treatment of ACS [17–20]. *In vitro* studies indicate that ticagrelor exerts its antiplatelet activity by binding to the $P2Y_{12}$ receptor at a site distinct from the adenosine diphosphate (ADP) binding site [21, 22], thereby inhibiting ADP-induced receptor signalling in a non-competitive manner [20]. Ticagrelor undergoes extensive hepatic metabolism, with one known active metabolite (AR-C124910XX) present at a concentration approximately 30% of the parent drug (R Teng *et al.*, unpublished data). Unlike the thienopyridines, however, ticagrelor does not require metabolic activation to exert its effect, which may account for its fast onset of action. Based on mass balance data, renal clearance of ticagrelor is limited and elimination occurs mainly through metabolism in the liver and biliary excretion (R Teng *et al.*, unpublished data).

Studies suggest that ticagrelor may provide improvements in IPA compared with clopidogrel [19, 23]. Compared with clopidogrel, ticagrelor offered a wider separation between antithrombotic effects and bleeding time in preclinical models and, in phase II studies, provided greater and more consistent inhibition of ADP-induced platelet aggregation without an increase in major plus minor bleeding. The efficacy and safety of ticagrelor has been evaluated in comparison with clopidogrel in a broad population of ACS patients, in the double-blind, randomized phase III PLATO (PLATelet inhibition and patient Outcomes) study [24, 25]. After 12 months, a lower proportion of patients receiving ticagrelor than clopidogrel reached the primary endpoint of death from vascular causes, myocardial infarction or stroke (9.8% *vs.* 11.7%; $P < 0.001$), with no increase in the rate of overall major bleeding and an increase in the rate of non-procedure-related bleeding [25].

Single ascending dose studies in healthy volunteers indicate that ticagrelor has linear pharmacokinetics and, at doses ranging from 100 to 400 mg, produces near-complete IPA at 2 h post-dose [26]. IPA gradually decreased with declining plasma concentrations starting around 12 h post-dose, indicating that the IPA associated with ticagrelor is concentration dependent and reversible.

The aims of this study were to evaluate the pharmacokinetics, pharmacodynamics and the safety and tolerability of multiple doses of ticagrelor dosed to steady-state in healthy volunteers and thereby establish the optimal dosing regimen for subsequent studies. As a comparator, a clopidogrel control arm was included (using the dose indicated for ACS in clinical practice) [27]. Although pharmacokinetic and pharmacodynamic data were collected, only pharmacodynamic data are reported.

Methods

Study population

The study enrolled healthy male and post-menopausal or surgically-sterile female volunteers between 18 and 65 years. Subjects were required to have a body mass index (BMI) between 18 and 30 kg m^{-2}, with a bodyweight >50 kg, and to be in good health based on physical examination, vital signs, laboratory values, and 12-lead electrocardiography (ECG) and have a bleeding time of <4 min (by lancet method). Exclusion criteria included: a history or presence of conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs, presence of clinically significant abnormal values for prothrombin or activated partial thromboplastin time, a history of intolerance or hypersensitivity to drugs or their excipients similar in chemical structure to ticagrelor (such as adenine nucleoside antivirals and immunosuppressant drugs), aspirin or other nonsteroidal anti-inflammatory drug use within 2 weeks of enrolment or treatment with any medication other than hormone replacement therapy within 3 weeks of dosing, a history of drug or alcohol abuse and tobacco use greater than 10 cigarettes per day or 12.5 g of tobacco per week or inability to abstain from tobacco use during treatment.

All subjects provided written informed consent, and the study was approved by an Independent Ethics Committee and performed in accordance with guidelines established by the Declaration of Helsinki.

Study design and treatment

This phase I study was a sequential, parallel-group, placebo-controlled, ascending dose study (D5130C05239) performed at a single centre to examine the pharmacoki-

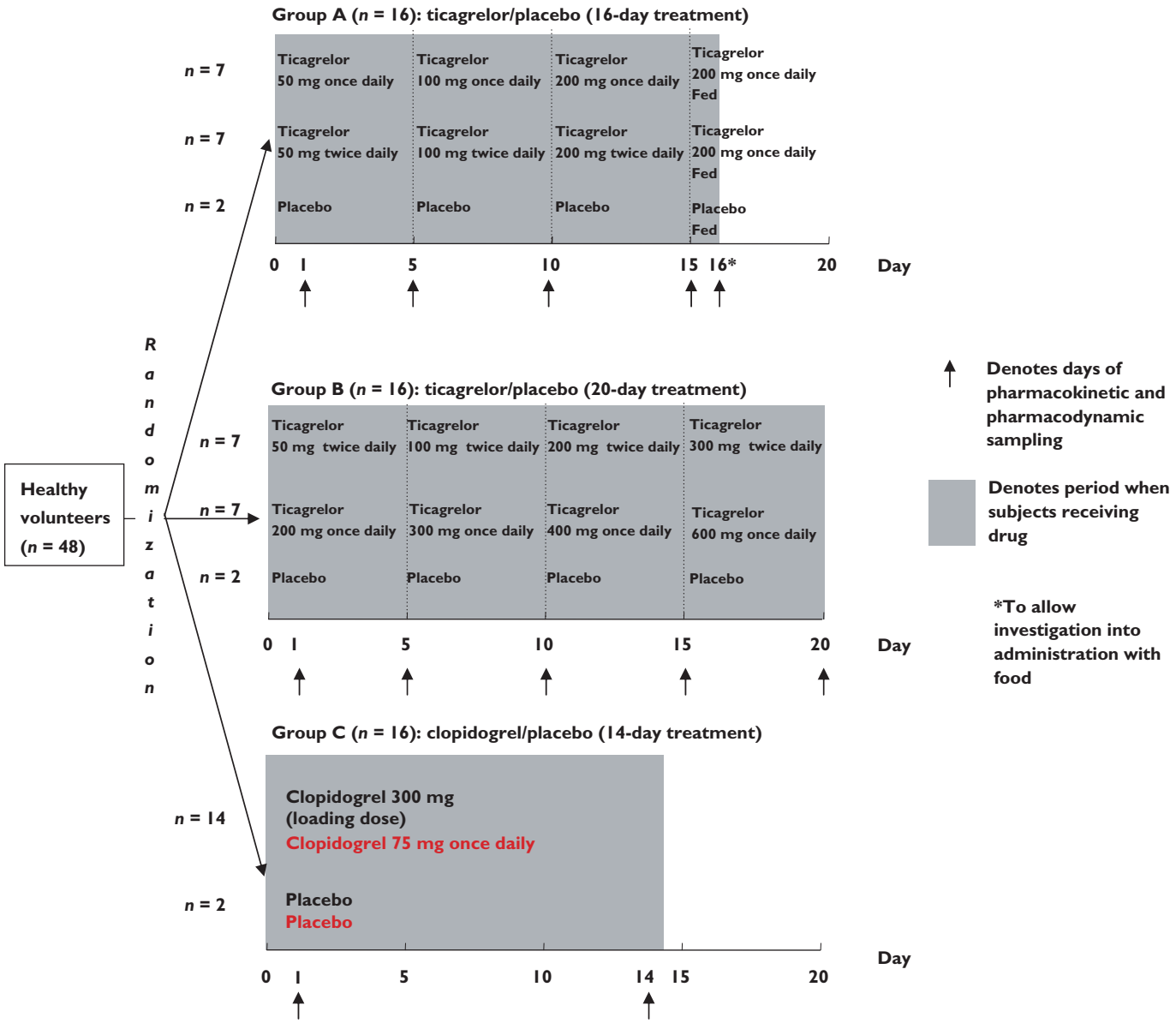

Figure 1
Study design

netics, pharmacodynamics, and safety and tolerability of ticagrelor. A clopidogrel control arm was included in the study to compare pharmacodynamic data with that of ticagrelor. Additionally, the carboxylic acid metabolite of clopidogrel was assayed to determine performance to published literature. Although due to the different dosing schedules and pharmacokinetic sampling times, it was not possible to allocate subjects blind to the ticagrelor and clopidogrel groups, placebo controls were used so subjects were unaware of whether they were receiving active or placebo treatments. In addition, ticagrelor was administered as a double-dummy, so subjects were unaware of whether they were receiving the once daily or twice-daily dosing regimen.

A total of 48 subjects were allocated to three groups (Figure 1), with assignment based on a strictly sequential randomization code. Two parallel groups of 16 subjects (groups A and B) received either placebo ($n = 2$) or ticagrelor ($n = 14$). Subjects received each ticagrelor dose (as tablets with 150 ml of water) for 5 days before escalation to the next dose level. A third group (group C) received either placebo ($n = 2$) or clopidogrel ($n = 14$) at the dose indicated for ACS in clinical practice [27].

Group A received ticagrelor at doses of 50, 100 and 200 mg once daily ($n = 7$) or ticagrelor at doses of 50, 100 and 200 mg twice daily ($n = 7$) or placebo ($n = 2$) for a total duration of 16 days. Group B received ticagrelor at doses of 50, 100, 200 and 300 mg twice ($n = 7$) or ticagrelor at doses

of 200, 300, 400 and 600 mg once daily ($n = 7$) or placebo ($n = 2$) for a total duration of 20 days. Before group B (scheduled to examine the higher ticagrelor doses) was initiated, Ggroup A was completed and the safety data reviewed before treatment of group B was allowed.

Early ticagrelor tablet formulations (50, 100 and 200 mg) were evaluated in this study and phase IIa studies [19, 28]. The phase III tablet formation (90 mg), which was also used in phase IIb and phase III PLATO studies, provided comparable ticagrelor exposure with the early tablet formulation (90 mg twice daily corresponded to 100 mg twice daily of the old formulation).

Group C received clopidogrel ($n = 14$) as an overencapsulated tablet at a 300 mg loading dose followed by 75 mg once daily for 14 days or placebo ($n = 2$) for a total duration of 14 days. Bioequivalence between the overencapsulated and intact tablets was demonstrated in a bioequivalence study in healthy subjects (AstraZeneca; data on file). To ensure blinding in those receiving ticagrelor once daily, subjects were administered placebo for the evening dose. Subjects were administered the morning dose of ticagrelor fasting and the evening dose with food. Clopidogrel doses were given in the fasting state (with 150 ml of water).

Blood sampling

Blood samples for pharmacokinetic (2–3 ml) and pharmacodynamic evaluation (4.5 ml) were collected at each dose level for the determination of ticagrelor and metabolite AR-C124910XX plasma concentrations. Pharmacokinetic sampling was performed on the days illustrated in Figure 1. Samples were collected on day 1 of the first dose level, and at day 5 at each ticagrelor dose level (corresponding to steady-state). After the pharmacokinetic sampling on day 5, subjects then received the next dose level. For clopidogrel, samples were collected on day 1 and at day 14.

Pharmacokinetic evaluations

Plasma concentrations of ticagrelor and AR-C124910XX were measured at 0 (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after the morning dose on the days of sampling. After the final study dose, measurements were also made 24 h after dosing. Blood samples were collected into lithium heparin tubes, centrifuged at 1500 *g* at 4°C for 10 min within 30 min of sampling. The resultant plasma was transferred into a plain polypropylene tube (screw cap) and stored at or below −20°C until analyzed.

Plasma concentrations of ticagrelor and AR-C124910XX were determined using a validated liquid chromatography and mass spectrometry detection after protein precipitation (H Sillén *et al.*, unpublished data). The method was validated using 0.1 ml plasma sample volumes for ticagrelor in the range of 1.0–500 ng ml^{-1} with a lower limit of quantification (LLOQ) of 1.0 ng ml^{-1} and for AR-C124910XX in the range of 2.5–500 ng ml^{-1} with a LLOQ of 2.5 ng ml^{-1}. The two assays provided accurate and reproducible results, with the defined limits of accuracy (standard deviation <20%) and precision (coefficient of variation <20% at the LLOQ and <15% at all other levels up to the upper limit of quantification).

Pharmacokinetic parameters

All pharmacokinetic calculations were performed with WinNonlin 3.2 Enterprise (Pharsight, Mountain View, CA, USA). Statistical analyses were carried out with SAS version 8 (SAS Institute, Inc., Cary, NC, USA).

The primary pharmacokinetic parameters were: peak plasma concentration (C_{max}); time to peak plasma concentration (t_{max}); area under the plasma concentration–time curve within the dosing interval (AUC(0,*t*)) on days 1 and 5, plasma elimination half-life ($t_{1/2}$) and apparent plasma clearance (CL/*F*). C_{max} was measured within 24 h after the last dose of once daily treatment and within 12 h after the last dose of twice daily treatment. t_{max} was defined as the time of first occurrence of C_{max}. Individual ticagrelor and AR-C124910XX $t_{1/2}$ values were calculated as $0.693/\lambda_z$, where λ_z is the terminal-phase elimination rate constant estimated by least-squares regression analysis of the plasma concentration–time data obtained over the terminal log-linear phase. AUC(0,*t*) was calculated by the trapezoidal rule and CL/*F* was calculated as dose divided by AUC(0,*t*).

The linearity of exposure to ticagrelor and AR-C124910XX *vs.* dose was assessed by fitting appropriate generaliszed linear models to AUC(0,12 h) for twice daily regimens, AUC(0,24 h) for once daily regimens, and C_{max} for both once daily and twice daily regimens. Accumulation ratios, calculated as the ratios of AUC(0,*t*) at steady-state (day 5) to AUC(0,*t*) on day 1, were expressed as geometric mean (coefficient of variation, %).

Pharmacodynamic evaluation

Inhibition of platelet aggregation was measured in blood samples obtained at 0 (pre-dose), 4, 8, 12 and 24 h on day 1, and at day 5 of each subsequent dose level in subjects receiving ticagrelor, and at 36 and 48 h after the first dose on the final study day in group B. IPA was measured at 0 (pre-dose), 4, 8, 12, and 24 h on day 1 and day 14 in subjects receiving clopidogrel.

Aggregation was performed according to the Born method [29]. This method produced similar reproducibility and precision to that previously described [29]. Blood was centrifuged at 180–200 *g* for 10 min, and the platelet-rich plasma (PRP) collected. PRP platelet count was adjusted to 300×10^9 l^{-1} using autologous platelet-poor plasma (PPP). Aggregation was measured continuously by light transmittance using ADP at final concentrations of 5 and 20 μmol L^{-1} (model 490D or 540Vs aggregometers, Chrono-log Corporation, Havertown, PA, USA). Autologous PPP and unstimulated PRP were used as 100% and 0% aggregation references, respectively. The maximal and final aggregation responses were reported. Percentage IPA was

calculated as 100 × ([mean pre-dose response − mean response during treatment visit]/mean pre-dose response). Percentage inhibition of optical aggregometry was summarized by treatment group and comparisons made between ticagrelor and clopidogrel.

Effect of food

To allow investigations into the food effect on pharmacokinetics and pharmacodynamics of ticagrelor, on day 16, subjects in group A received ticagrelor 200 mg with food. In this group, subjects received only a morning dose on the final day of the 16-day treatment period with a high-fat breakfast (Figure 1). The effect of food was then assessed by informal comparison of pharmacokinetic data obtained in the fasting and fed states in subjects receiving ticagrelor 200 mg once daily or twice daily in group A.

Bleeding times

Standard lancet bleeding times were assessed throughout the study, using the Simplate method at a distending venous pressure of 40 mmHg applied with a standard sphygmomanometer cuff. Blood was blotted in a systematic manner with a filter paper every 30 s noting the time (to nearest 15 s) when bleeding had ceased. For subjects taking ticagrelor, measurements were determined at enrolment, on admission (day 0), day 1, at 0 (pre-dose), 4 and 11 h after first dose, days 4 and 9, at 11 h post-dose, day 15, at 0, 4 and 11 h after the first dose and (group B only) day 20, at 0, 4 and 11 h after first dose. For group C, measurements were determined at enrolment, on admission, day 1, at 0, 4 and 11 h after first dose and days 1, 7 and 14 at 11 h post-dose. Bleeding time data were summarized by treatment group and comparisons were made between ticagrelor and clopidogrel groups.

Safety and tolerability

Safety evaluation included recording of adverse events, physical examination, assessment of vital signs, ECG, clinical chemistry and haematology assessments, and urinalysis. Samples for laboratory analysis were obtained prior to the first study dose, pre-dose at the start of each dose level, 48 h after the first dose on the last day of study dosing and at a follow-up visit 7 to 14 days after completion of study treatment. Safety results were summarized by treatment group.

Results

A total of 48 subjects (90% male, 92% Caucasian) were enrolled in the study. The mean age of the study population was 37 years (range 20–64 years), and mean weight was 75 ± 10.7 kg. Twenty-eight subjects received ticagrelor (groups A and B), and 14 subjects received clopidogrel (300 mg loading dose followed by 75 mg once daily). Two subjects in each group received placebo (groups A and B, ticagrelor placebo; group C, clopidogrel placebo). The mean age of subjects in groups A, B and C was 43 (± 17.7), 33 (± 10.6) and 35 (± 11.3) years, respectively; mean weight was 72 (± 11.5), 73 (± 8.3) and 81 (± 10.1) kg, respectively.

Pharmacokinetics of ticagrelor and AR-C124910XX

Calculated pharmacokinetic parameters and their variability are shown in Table 1.

Single dose pharmacokinetics

After a single dose (day 1), comparison of ticagrelor 50 mg and 200 mg once daily showed that the mean C_{max} and AUC(0,*t*) for ticagrelor increased in proportion to dose. Ticagrelor was rapidly absorbed and the median t_{max} was 2 h. Mean ticagrelor $t_{1/2}$ after a single dose ranged from 6.2 to 6.9 h (Table 1). Mean apparent clearance ranged from 293 to 374 ml min^{-1}.

Comparison of the ticagrelor 50 mg and 200 mg once daily showed that the mean C_{max} and AUC(0,*t*) of AR-C124910XX also increased in proportion to dose. Overall, exposure to the active metabolite AR-C124910XX was approximately 40% of exposure to ticagrelor. Formation of AR-C124910XX was rapid (day 1, median t_{max} 2.5–4.0 h over the range of ticagrelor doses). The mean elimination $t_{1/2}$ of AR-C124910XX after a single dose ranged from 6.4 to 9.4 h (Table 1). Plasma concentrations of clopidogrel (300 mg loading dose followed by 75 mg once daily) were consistent with those previously reported [19, 23, 28].

Steady-state pharmacokinetics

Mean plasma concentration–time profiles of ticagrelor (Figure 2A,B) and AR-C124910XX (Figure 3A,B) at steady-state (day 5) demonstrated that after multiple dosing with both once daily and twice daily ticagrelor, increasing ticagrelor dose resulted in increases in the AUC(0,*t*) and C_{max}. At day 5, median t_{max} of ticagrelor ranged from 1.5–3.0 h for once daily and 2–3 h for twice daily over the range of ticagrelor doses (Table 1). Mean apparent clearance was consistent over both once daily (range 388–471 ml min^{-1}) and twice daily dosing (range 362–511 ml min^{-1}). Mean ticagrelor $t_{1/2}$ determined at steady-state ranged from 7.7 to 13.1 h with once daily dosing and from 6.7 to 9.1 h with twice daily dosing.

After multiple dosing, exposure to AR-C124910XX was approximately 40% of exposure to ticagrelor (Table 1). Formation of AR-C124910XX was again rapid (median t_{max} 2.0–4.0 h over the range of once daily and twice daily ticagrelor doses). The mean elimination $t_{1/2}$ of AR-C124910XX at steady-state ranged from 7.5 to 12.4 h (twice daily and once daily dosing).

Further analysis of the dose proportionality of the pharmacokinetics of ticagrelor and AR-C124910XX showed

Table 1

Pharmacokinetics of ticagrelor and its main metabolite AR-C124910XX on day 1 and at end of dosing period (day 5) at doses of 50–600 mg once daily and 50–300 mg twice daily

Ticagrelor dose (mg)	C_{max} (ng ml^{-1}) Day 1	C_{max} (ng ml^{-1}) Day 5	t_{max} (h) Day 1	t_{max} (h) Day 5	AUC(0,t) (ng ml^{-1} h) Day 1	AUC(0,t) (ng ml^{-1} h) Day 5	CL/F (ml min^{-1}) Day 1	CL/F (ml min^{-1}) Day 5	$t_{1/2}$ (h) Day 1	$t_{1/2}$ (h) Day 5	Accumulation ratios, Day 5 : Day 1
Once daily dosing											
Ticagrelor											
50 (n = 7)	219 (60)	222 (33)	2 (1.5–6)	3 (2–4)	1,531 (40)	1,877 (34)	293 (37)	417 (32)	6.9 (16)	7.7 (27)	1.2 (15)
100 (n = 7)	–	557 (50)	–	3 (1.5–4)	–	4,295 (43)	–	388 (43)	–	7.8 (22)	–
200 (n = 7, 14)*	785 (27)	1,030 (42)	2 (1.5–4)	2 (1.5–4)	4,970 (29)	7,884 (48)	336 (32)	423 (48)	6.2 (12)	8.2 (28)	1.2 (16)
300 (n = 7)	–	1,354 (23)	–	1.5 (1.5–2)	–	10,611 (32)	–	471 (32)	–	7.8 (26)	–
400 (n = 6)	–	1,862 (12)	–	1.5 (1–2)	–	14,963 (26)	–	446 (26)	–	8.6 (35)	–
600 (n = 6)	–	2,958 (33)	–	1.75 (1–3)	–	24,088 (33)	–	415 (33)	–	13.1 (23)	–
AR-C124910XX											
50 (n = 7)	57 (65)	71 (40)	4 (2–8)	3 (3–6)	542 (52)	744 (40)	–	–	9.4 (20)	10.6 (36)	1.4 (22)
100 (n = 7)	–	171 (50)	–	4 (2–4)	–	1,880 (42)	–	–	–	11.3 (20)	–
200 (n = 7, 14)*	215 (36)	293 (45)	3 (1.5–4)	3 (2–4.12)	1,671 (40)	3,053 (48)	–	–	8.0 (20)	12.5 (46)	1.3 (15)
300 (n = 7)	–	362 (31)	–	2 (1.5–3)	–	3,941 (26)	–	–	–	9.9 (8)	–
400 (n = 6)	–	508 (15)	–	2 (2–3)	–	5,577 (31)	–	–	–	12.3 (39)	–
600, day 5 (n = 6)	–	791 (30)	–	2.5 (1.5–3)	–	8,962 (34)	–	–	–	16.6 (19)	–
Twice daily dosing											
Ticagrelor											
50 (n = 14)	172 (38)	251 (34)	2 (1.5–4)	3 (1–4)	942 (37)	1,682 (35)	374 (58)	511 (36)	6.6 (3.3)	6.7 (28)	1.8 (27)
100 (n = 13)	–	626 (46)	–	2 (1–6)	–	4,108 (43)	–	406 (45)	–	6.7 (45)	–
200 (n = 13)	–	1,440 (27)	–	2 (1.5–4)	–	9,436 (30)	–	362 (32)	–	9.1 (62)	–
300 (n = 7)	–	1,936 (69)	–	3 (2–4)	–	14,203 (54)	–	378 (55)	–	8.6 (37)	–
AR-C124910XX											
50 (n = 14)	55 (39)	81 (28)	2.5 (2–4)	3 (1.5–6)	336 (35)	639 (29)	–	–	6.4 (37)	7.5 (25)	1.9 (28)
100 (n = 13)	–	219 (49)	–	3 (1.5–6)	–	1,701 (47)	–	–	–	9.2 (95)	–
200 (n = 13)	–	462 (48)	–	3 (1.5–6)	–	3,693 (49)	–	–	–	12.4 (54)	–
300 (n = 7)	–	592 (42)	–	3 (2–4)	–	5,111 (31)	–	–	–	10.7 (49)	–

Data for t_{max} are median (range); all other data are geometric mean (coefficient of variation, %). *n = 7 for day 1, n = 14 for day 5.

that the pharmacokinetics were predictable. Mean C_{max} and AUC(0,t) (AUC(0,12 h) for twice daily dosing and AUC(0,24 h) for once daily dosing) for ticagrelor and AR-C124910XX increased dose proportionately (Figure 4A,B). With a twofold increase in ticagrelor dose, 2.37- and 2.32-fold increases were seen in the AUC(0,t) of ticagrelor and AR-C124910XX, with approximately a 2.2-fold increase in C_{max} with a doubling of the dose.

Accumulation ratios (geometric mean [coefficient of variation, %]), expressed as the ratios of AUC(0,t) on day 5 to AUC(0,t) on day 1, were 1.2 for ticagrelor 50 mg and 200 mg once daily and 1.8 for 50 mg twice daily. For AR-C124910XX, accumulation ratios were 1.4, 1.3 and 1.9, respectively (Table 1).

Pharmacodynamics

The pattern of results was similar irrespective of whether IPA was assessed from the final extent of aggregation (observed at the end of the platelet response) or from the maximal extent of aggregation. Hence, only final extent of IPA responses (which tends to be more sensitive to $P2Y_{12}$ receptor antagonists as it is mediated primarily by the $P2Y_{12}$ receptor) [30] are shown.

Peak mean final extent IPA (80–100%, 20 μM ADP) at all doses of ticagrelor was observed at the first post-dose measurement (4 h) on day 1 (Figure 5A) and day 5 (Figure 5B,C). At all ticagrelor doses, substantial IPA was seen, although increasing levels of inhibition and duration of response were seen with increasing once daily and twice daily doses (Figure 5C,B, respectively). IPA was greater and more consistently sustained at high levels over the dosing interval with ticagrelor twice daily than with once daily dosing (Figure 5B,C, respectively).

Ticagrelor twice daily doses resulted in higher mean IPA than the equivalent once daily dosing. At trough plasma drug concentrations (24 h, day 5), mean IPA (final extent) was greater with ticagrelor 100 mg twice daily (93%) compared with ticagrelor 200 mg once daily (76%); mean IPA was 97% with ticagrelor 200 mg twice daily compared with 400 mg once daily (90%); mean IPA was 100% with ticagrelor 300 mg twice daily compared with 600 mg once daily (91%).

IPA levels with ticagrelor doses of ≥300 mg once daily and ≥100 mg twice daily were higher and more sustained over the measured dose interval than those with clopidogrel (300 mg loading dose followed by 75 mg once daily; Figures 5B,C, respectively). At trough plasma drug concentrations (24 h, day 5), mean IPA (final extent) was 82–91% (range 61–100%) for ticagrelor ≥300 mg twice daily and 93–100% (range 65–100%) for ticagrelor ≥100 mg twice daily, compared with 77% (range 11–100%) after 14 days of clopidogrel. IPA with clopidogrel

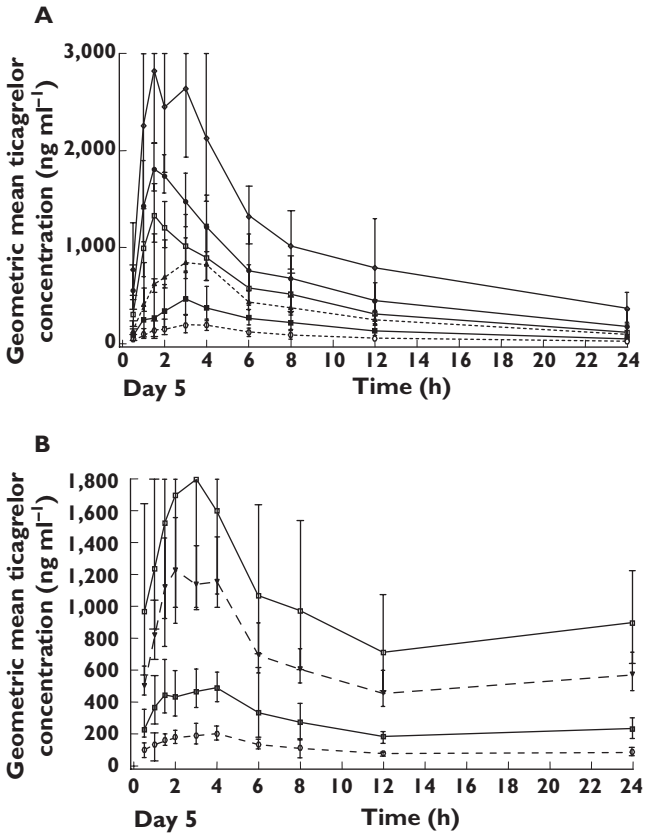

Figure 2

Geometric mean (± 95% CI) plasma concentrations of ticagrelor after A) ticagrelor once daily dosing and B) ticagrelor twice daily dosing on day 5. (A) 50 mg once daily (- -○- -); 100 mg once daily (—■—); 200 mg once daily (- -▲- -); 300 mg once daily (—□—); 400 mg once daily (—●—); 600 mg once daily (—◆—). (B) 50 mg twice daily (- -○- -); 100 mg twice daily (—■—); 200 mg twice daily (– ▼ –); 300 mg twice daily (—□—)

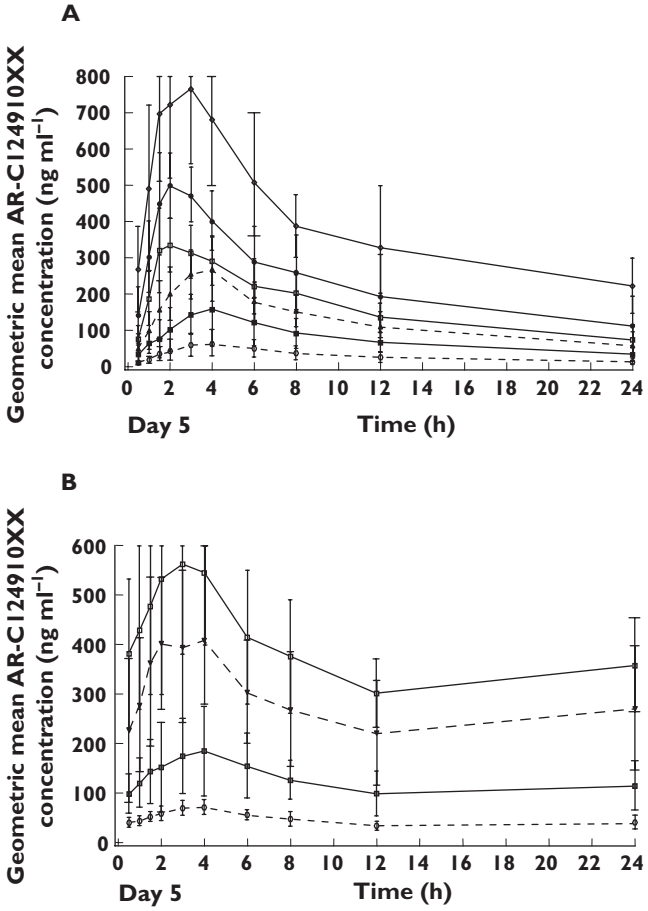

Figure 3

Geometric mean (± 95% CI) plasma concentrations of AR-C124910XX after A) ticagrelor once daily dosing and B) ticagrelor twice daily dosing on day 5. (A) 50 mg once daily (- -○- -); 100 mg once daily (—■—); 200 mg once daily (- -▲- -); 300 mg once daily (—□—); 400 mg once daily (—●—); 600 mg once daily (—◆—). (B) 50 mg twice daily (- -○- -); 100 mg twice daily (—■—); 200 mg twice daily (– ▼ –); 300 mg twice daily (—□—)

was in line with expectations based on previously reported data [19, 23, 28].

Figure 6 indicates that increasing plasma concentrations of ticagrelor were associated with increasing IPA. At lower ticagrelor plasma concentrations, the extent of IPA was considerable, ranging from (0–100%). A similar relationship was seen with AR-C124910XX plasma concentrations and IPA (data not shown).

Effect of food

Administration of ticagrelor 200 mg (once daily or twice daily) with food resulted in an approximately 25% increase in ticagrelor exposure (Table 2). For ticagrelor 200 mg once daily, AUC(0,*t*) increased 20%, from 10 603 ng ml^{-1} h (fasting state) to 12 768 ng ml^{-1} h (fed state). Also, C_{max} increased 17% when administered with food. For subjects receiving ticagrelor 200 mg twice daily, AUC(0,*t*) increased 31%, from 10 160 ng ml^{-1} h (fasting state) to 13 335 ng ml^{-1} h (fed state). C_{max} increased 11% when administered with food. Administration of ticagrelor 200 mg (once daily or twice daily) with food had no apparent effect on exposure to AR-C124910XX compared with fasting administration. Administration of food with ticagrelor had no apparent effect on the final extent of IPA (Table 2).

Bleeding times

Median baseline bleeding time was 165 s (range 128–263 s). Compared with baseline, median bleeding times increased with ticagrelor by approximately 1.1- to 3.3-fold, compared with a 1.1- to 1.2-fold increase with placebo, and a 1.5- to 1.9-fold increase with clopidogrel. On two occasions, individual bleeding times at scheduled timepoints exceeded 30 min (on day 4 in one subject receiving ticagrelor 100 mg twice daily and on day 14 in one subject receiving clopidogrel 75 mg once daily). Other bleeding times measured for these subjects were less than 10 min.

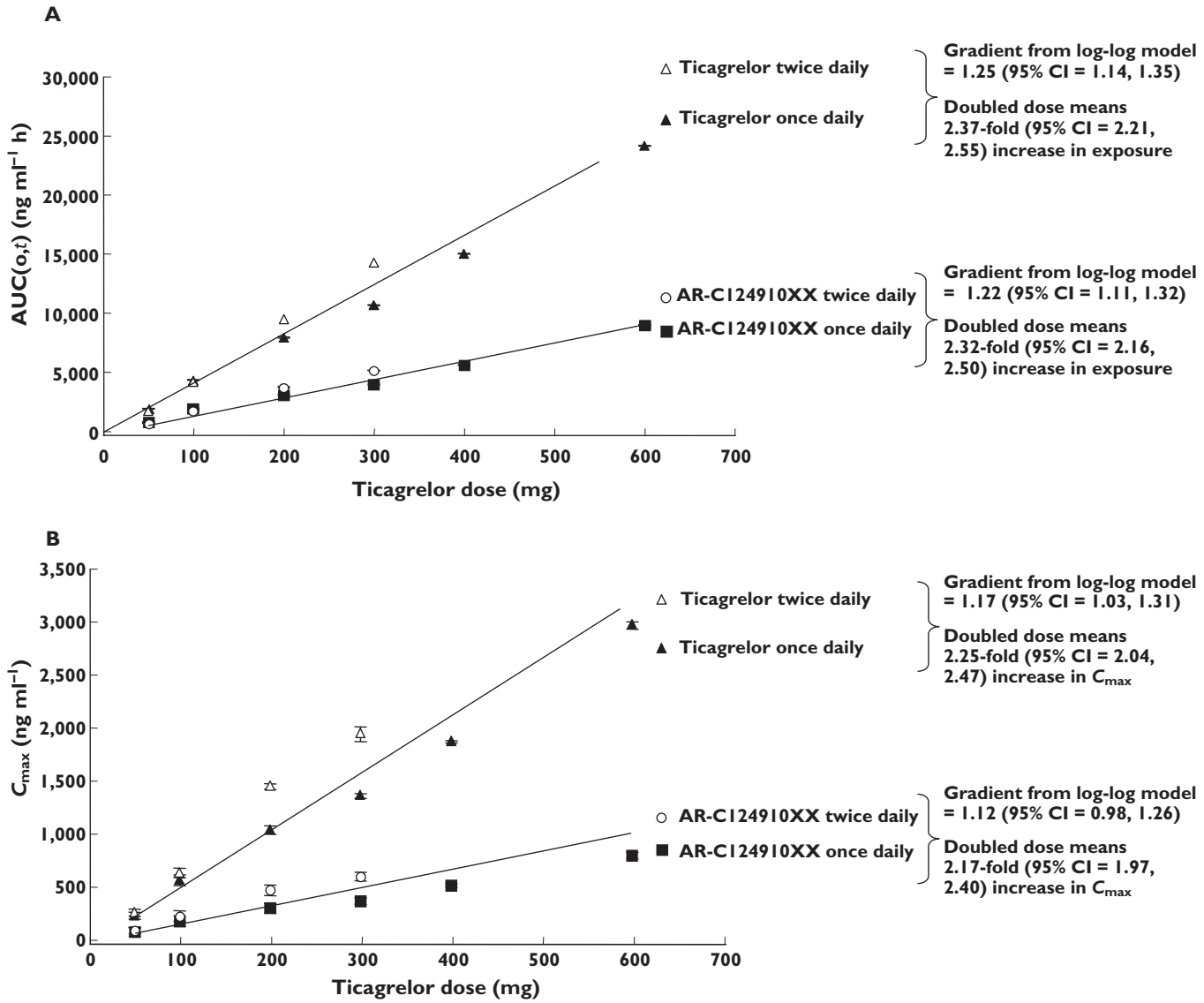

Figure 4

Analysis of pharmacokinetic dose-proportionality: effect of increasing ticagrelor dose (administered either as once daily or twice daily) on A) AUC(0,*t*) of ticagrelor and AR-C124910XX and B) C_{max} of ticagrelor and AR-C124910XX. Data expressed as geometric mean ± 95% CV gradient determined from log-log model

There was no clear dose or plasma concentration relationship with bleeding times (data not shown).

Safety and tolerability

Thirty subjects in groups A and B completed study treatment, with two discontinuing due to adverse events. All subjects in group C completed study treatment.

Adverse events observed with ticagrelor, administered at various dosing schedules, were comparable with those observed with once daily clopidogrel. Study treatments were well tolerated with no serious, severe, or dose-related adverse events reported. The most common adverse events considered possibly related to study treatment were myalgia in three subjects receiving ticagrelor, and gingival bleeding in two subjects on clopidogrel, and one on ticagrelor. No subjects in the study reported dyspnoea.

Two subjects receiving ticagrelor discontinued treatment due to adverse events. One subject was withdrawn from the study due to elevated alanine (ALT) and aspartate transaminase (AST) concentrations (ALT 266 IU l^{-1} and AST 141 IU l^{-1}), which were three times the upper limit of normal following 4 days of treatment with ticagrelor 300 mg once daily. By day 24, transaminase concentrations were below 100 IU l^{-1}, and were normal at 10-day follow-up in this subject. There was no associated rise in bilirubin or alkaline phosphatase, and no other causative aetiology was determined. A second subject on ticagrelor withdrew due to asthma/bronchitis, considered unrelated to study

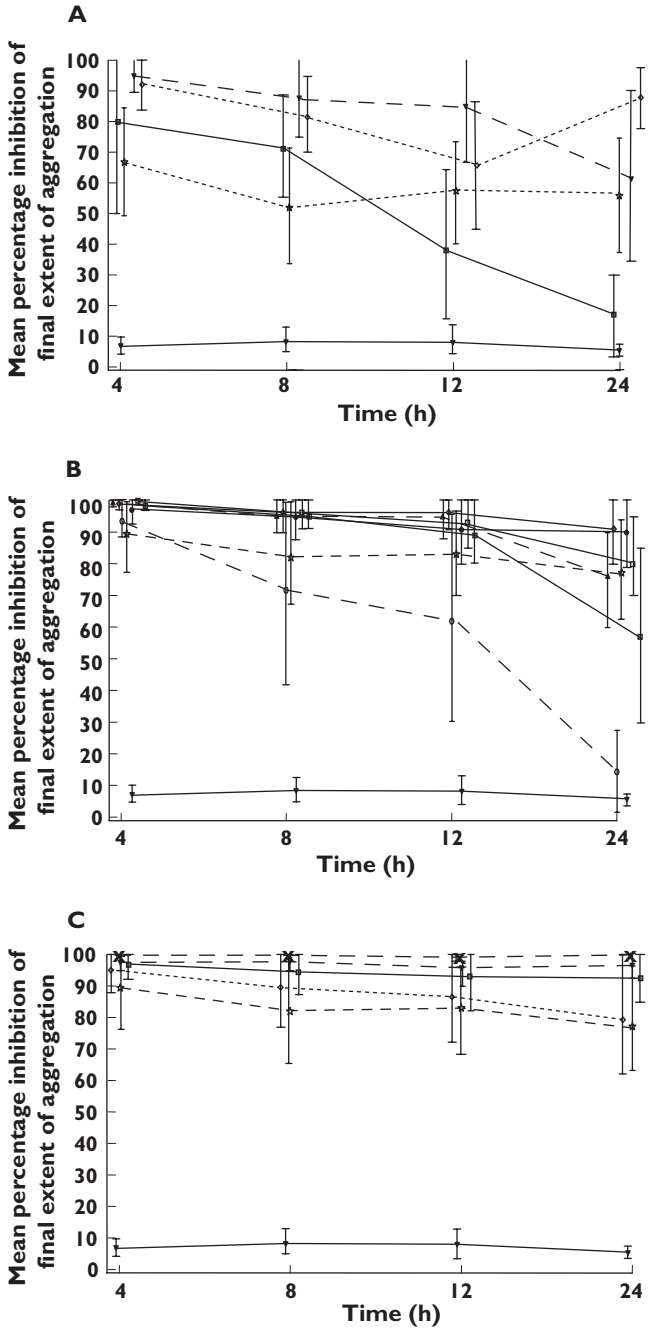

Figure 5

Mean % IPA (± 95% CI) over time at final extent (aggregation (optical aggregometry, 20 μM ADP) after ticagrelor (multiple doses) and clopidogrel (loading dose 300 mg followed by 75 mg once daily) after a single dose (day 1) (A) and at steady-state (ticagrelor, day 5; clopidogrel, day 14) (B and C). Figure 5B shows ticagrelor once daily doses; Figure 5C shows ticagrelor twice daily doses. Footnote: data were collected at timepoints 4, 8, 12 and 24 h, but are offset to avoid overlap. (A) 50 mg twice daily (◇); 200 mg once daily (– ▼ –); Clopidogrel 75 mg once daily (- ☆ -); 50 mg once daily (—■—); Placebo (—▼—). (B) 600 mg once daily (—◆—); 400 mg once daily (—●—); 300 mg once daily (—□—); Clopidogrel 75 mg once daily (- ☆ -); 200 mg once daily (- ▲ -); 100 mg once daily (—■—); 50 mg once daily (- ○ -); Placebo (—▼—). (C) 300 mg twice daily (– X –); 200 mg twice daily (– ▼ –); 100 mg twice daily (—■—); 50 mg twice daily (◇); Clopidogrel 75 mg once daily (- ☆ -); Placebo (—▼—)

treatment. Another subject had a clinically relevant increase in ALT and AST concentrations (110 IU l^{-1} and 64 IU l^{-1}, respectively) on study day 15 following 4 days of treatment with ticagrelor 200 mg twice daily. This adverse event was mild in severity, and the subject continued treatment. Transaminase concentrations improved in this subject during 300 mg once daily dosing and were resolved in 14 days. Baseline levels for both subjects with elevated transaminase levels were within the upper limit of normal. A causal relationship between the study drug and the increase in levels was considered reasonably possible. No other clinically relevant changes in vital signs, ECG, or laboratory values were observed.

Discussion

This multiple ascending dose study showed that the pharmacokinetics of ticagrelor are linear and stationary over the dose range of 50–600 mg once daily and 50–300 mg twice daily. The pharmacokinetics of ticagrelor and its metabolite behaved in a predictable manner with C_{max} and AUC(0,t) increasing approximately dose-proportionally with increasing dose (approximately 2.2- to 2.4-fold with a twofold increase in dose). The $t_{1/2}$ and t_{max} of ticagrelor and its active metabolite AR-C124910XX were independent of ticagrelor dose, as was the CL/F of ticagrelor. Consistent with the results of other pharmacokinetic studies over a range of ticagrelor doses [31], ticagrelor demonstrates a predictable and linear pharmacokinetic profile that would make it easy to use in clinical practice.

The finding that the magnitude of IPA was associated with plasma ticagrelor concentrations is to be expected, since ticagrelor exerts its antiplatelet activity by binding directly to the $P2Y_{12}$ receptor. This mechanism is in contrast to the thienopyridines, clopidogrel and prasugrel, that must undergo metabolic conversion in order to exert activity. Our pharmacokinetic data showed that the absorption of ticagrelor was rapid, with mean t_{max} of 2 h. This finding is consistent with previous data showing that the onset of the antiplatelet effect of ticagrelor occurs within approximately 30 min [19, 32, 33]. As the first measurement of IPA was not performed until 4 h, our study was not suitable to characterize fully the early onset of the effect of ticagrelor, but our data support previous findings that the onset of peak inhibitory activity is faster with ticagrelor than with the standard clopidogrel dose [14, 19, 23, 33]. IPA was not measured with clopidogrel until day 14 in our study, since even with a loading dose, clopidogrel does not achieve full platelet activity for 4–8 days [34].

In addition to the rapid onset of effect, *in vitro* binding studies have shown that ticagrelor binds reversibly to the $P2Y_{12}$ receptor [21, 22]. Thus, a more rapid recovery of function of existing platelets would be expected, compared with the irreversibly binding thienopyridines (whose recovery of platelet function depends on regeneration of

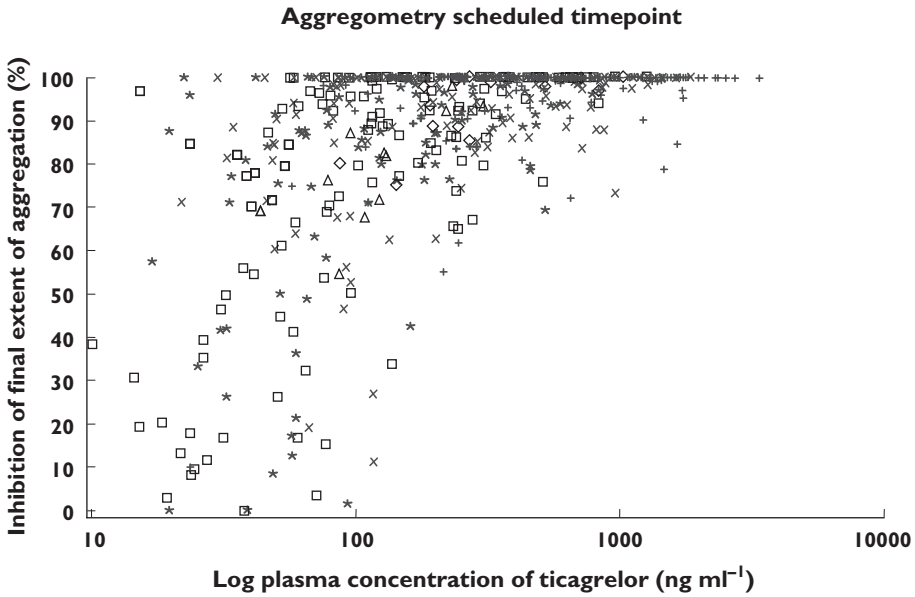

Figure 6

Effect of log ticagrelor plasma concentration on % IPA (final extent, 20 μM ADP). Data shown over a restricted plasma concentration range (0–1000 ng ml^{-1}); key shows actual time (post-dose) of aggregometry measurement. 4 h (+); 8 h (×); 12 h (*); 24 h (□); 36 h (◇); 48 h (△)

Table 2

Effect of administration with food compared with fasting on pharmacokinetics of ticagrelor and AR-C124910XX and % IPA (Final Extent, 20 μM ADP) after administration of ticagrelor 200 mg once daily or bid

	Pharmacokinetics			Mean % IPA (range)			
	AUC(0,τ) (ng ml^{-1} h)	C_{max} (ng ml^{-1})	t_{max} (h)	4 h	8 h	12 h	24 h
Once daily ticagrelor							
200 mg, fasting, day 5 (*n* = 7)	10 603 (41)	1304 (44)	3.00 (1.50–4.00)	99 (97–100)	98 (93–100)	98 (91–100)	89 (67–100)
200 mg, fed, Day 1 (*n* = 7)	12 768 (42)	1525 (39)	3.00 (1.33–4.00)	100 (100–100)	95 (86–100)	97 (89–100)	80 (34–100)
Twice daily ticagrelor							
200 mg, fasting, day 5 (*n* = 6)	10 160 (26)	1583 (26)	2.00 (2.00–4.00)	97 (85–100)	98 (89–100)	96 (79–100)	96 (76–100)
200 mg, fed, day 1 (*n* = 6)	13 335 (14)	1763 (24)	4.00 (3.00–12.00)	96 (79–100)	95 (73–100)	95 (69–100)	94 (66–100)
AR-C124910XX (after once daily dosing)							
200 mg, fasting, day 5 (*n* = 7)	4 164 (35)	385 (35)	4.00 (2.00–4.12)	–	–	–	–
200 mg, fed, day 1 (*n* = 7)	4 079 (39)	358 (23)	4.00 (1.83–6.00)	–	–	–	–
AR-C124910XX (after twice daily dosing)							
200 mg, fasting, day 5 (*n* = 6)	4 423 (71)	555 (65)	3.50 (2.00–4.00)	–	–	–	–
200 mg, fed, day 1 (*n* = 6)	4 887 (56)	568 (52)	5.00 (3.00–12.00)	–	–	–	–

Data for t_{max} are median (range); all other pharmacokinetic data are geometric mean (coefficient of variation, %).

platelets) [35]. Indeed, the European Society of Cardiology guidelines recommend that coronary artery bypass surgery should be postponed for 5 days in patients pretreated with clopidogrel [1]. Therefore, antiplatelet agents with rapid recovery of platelet function would provide greater flexibility for surgery.

The plasma concentrations of clopidogrel and associated degree of IPA observed in our study were consistent with the expected effects based on published results with clopidogrel at the 300 mg loading dose followed by 75 mg once daily [19, 23, 28]. The superior antiplatelet activity of ticagrelor at doses ≥50 mg twice daily over the standard clopidogrel dose is also consistent with previously published data [19, 23, 28]. In the randomized, double-blind, phase IIb DISPERSE2 trial in 900 patients with ACS, ticagrelor 90 mg twice daily over 12 weeks produced a level of platelet inhibition that was almost double that of standard treatment with clopidogrel [28]. A pharmacodynamic substudy of DISPERSE2 in 89 patients showed that after 4 weeks, both ticagrelor 90 mg twice daily and ticagrelor 180 mg twice daily demonstrated a greater mean IPA (79% and 95%, respectively; 4 h final aggregation response) than

standard clopidogrel treatment (64%) [23]. In addition, a double-blind, randomized, phase II trial in 200 patients with stable atherosclerosis demonstrated that both ticagrelor 100 mg and 200 mg twice daily in combination with aspirin (75–100 mg once daily) had superior antiplatelet efficacy to clopidogrel 75 mg once daily plus aspirin over 28 days of treatment [19].

Our finding that the extent of IPA over the dosing interval was greater with ticagrelor doses of ≥50 mg twice daily than with the standard dose of clopidogrel (300 mg loading dose followed by 75 mg once daily) is in agreement with previous data showing that clopidogrel only moderately inhibits platelet aggregation in response to ADP [19, 36]. In addition, we showed that the range of responses with clopidogrel at steady-state with standard dosing was variable. We acknowledge the large variability in all IPA measurements as well as the small number of patients in this study arm ($n = 14$), but these data are consistent with the wide variability in responses to clopidogrel (approximately 15–48% of patients have a poor platelet inhibition response) [3–6].

One concern with superior inhibition of platelet activity is the potential hazard of additional bleeding. However, in our study, there were no notable differences in bleeding time between any ticagrelor dosing regimen and clopidogrel (300 mg loading dose followed by 75 mg once daily) based on median bleeding times for each regimen. Moreover, phase II and phase III data showed that the increased level of platelet inhibition was not associated with any substantial increase in bleeding with ticagrelor, compared with clopidogrel [25, 28]. Although ticagrelor did show an increase in minor bleeding compared with clopidogrel, there was no difference in major bleeding.

The superior responses with ticagrelor twice daily dosing compared with once daily administration support the selection of a twice daily regimen as the optimal dosing regimen for subsequent phase II and phase III studies [25, 28]. To accelerate further the onset of antiplatelet activity, ticagrelor is given as a loading dose of 180 mg followed by 90 mg twice daily (selected due to its tolerability and significantly improved IPA over clopidogrel [23, 28]), which has been compared with clopidogrel in the PLATO trial [25]. As a result of the improved potency of ticagrelor over clopidogrel, the degree of IPA with ticagrelor in the present study was greater than with clopidogrel, consistent with the efficacy results observed in the PLATO study.

Administration with food resulted in a small increase in exposure to ticagrelor, though there was no apparent effect on exposure to the metabolite AR-C124910XX. Due to the exploratory nature of the food effect evaluation in this study, no definitive conclusions regarding the magnitude of the effect of food can be estimated from these data. However, in a previous study designed specifically to assess the effect of food on ticagrelor pharmacokinetics with the proposed commercial tablet formulation, consumption of a standard high-fat meal resulted in a 21% increase in ticagrelor AUC(0,∞) and a 22% decrease in AR-C124910XX C_{max}, with no effect on ticagrelor C_{max} or AR-C124910XX AUC(0,∞) [37]. As these changes are considered of minimal clinical significance, these preliminary results suggest that ticagrelor can be administered with or without food. Consequently, ticagrelor was administered in the clinical development studies without consideration of food intake.

Data from the present study indicate that treatment with oral ticagrelor at doses up to 600 mg day^{-1} was well tolerated in healthy volunteers. Ticagrelor had a similar adverse event profile to clopidogrel, with no serious, severe, or dose-related adverse events reported. There were transient increases in transaminase concentrations in two subjects receiving ticagrelor (300 mg once daily and 200 mg twice daily). However, increased liver transaminase concentrations have not been reported in other studies with ticagrelor [19, 28]. While the potential for an effect of high plasma concentrations of ticagrelor on hepatic function in those patients cannot be ruled out, the doses received by these two patients were higher than would be used in clinical practice. Notably, in the PLATO study carried out in over 18 000 patients [25], transaminase elevations were not identified as one of the major laboratory abnormalities with 90 mg twice daily ticagrelor. No clinically important effects on other laboratory parameters, vital signs or ECG were observed. Phase III studies in a greater number of subjects and in patients with ACS will clarify these findings.

In conclusion, our findings illustrate that the pharmacokinetics of ticagrelor are predictable, and are associated with consistent inhibition of platelet activity, to a greater extent than clopidogrel. The rapid onset of activity of ticagrelor coupled with a fast rate of platelet recovery may offer several advantages to patients with ACS.

Competing interests

KB and RT are current employees of AstraZeneca.

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