A multiple dose study of prasugrel (CS-747), a novel thienopyridine P2Y₁₂ inhibitor, compared with clopidogrel in healthy humans

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Aims

This double-blind, placebo-controlled trial was designed to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y₁₂ ADP receptor antagonist compared with clopidogrel, during multiple oral dosing in healthy subjects.

Methods

Thirty subjects received placebo, prasugrel 5 mg, 10 mg, or 20 mg, or clopidogrel 75 mg orally, daily for 10 days. Platelet aggregation, bleeding time, and prasugrel metabolites were measured and adverse events were recorded.

Results

Inhibition of ADP-induced platelet aggregation reached steady state by day 3 following prasugrel 10 and 20 mg compared with 5 days for clopidogrel 75 mg or prasugrel 5 mg. Compared with placebo, at 24 h after the last dose of study drug, inhibition of platelet aggregation using (20 µM) ADP was significantly higher in the prasugrel 10 mg group (58.2 ± 4.9% vs. 9.2 ± 4.0%, $P < 0.001$) with no difference in the clopidogrel group (15.7 ± 6.8% vs. 9.2 ± 4.0%, $P = 0.78$). With 5 µM ADP, inhibition of platelet aggregation with prasugrel 10 mg and clopidogrel 75 mg was significantly higher than with placebo (prasugrel 10 mg, 70.5 ± 4.7%; clopidogrel 75 mg, 36.5 ± 9.0%; vs. placebo, 11.3 ± 5.1%; $P < 0.0001$ and $P = 0.02$). On day 10 at 4 h postdose, bleeding time was prolonged with prasugrel 10 mg (prasugrel 10 mg, 706 ± 252 s vs. placebo, 221 ± 38 s, $P = 0.05$) but not with clopidogrel (283 ± 56 s, $P = 0.98$). There were no clinically significant bleeding events, serious adverse events, or discontinuations of the study drug.

Conclusions

Compared with clopidogrel 75 mg, prasugrel 10 mg and 20 mg daily for 10 days resulted in more rapid, more consistent, and higher levels of platelet inhibition.

Introduction

Platelet activation and aggregation play a central role in atherothrombotic vascular disease [1, 2]. Platelets are exposed to the subendothelial matrix at the sites of ath-

erosclerotic plaque rupture, allowing adhesion to matrix proteins including collagen and von Willebrand factor. Activation of the platelets by these interactions results in release of adenosine 5'-diphosphate (ADP) which can

induce secondary platelet activation and aggregation through ADP-induced platelet activation via the G-protein linked P2Y₁₂ and P2Y₁ receptors, further amplifying and propagating platelet activation induced by the primary activators [3–6]. Activated platelets are recruited to sites of coronary plaque rupture forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischaemia, and necrosis in what is collectively known as acute coronary syndrome (ACS) [7, 8]. A number of studies have demonstrated the effectiveness of the thienopyridines, a class of P2Y₁₂ ADP receptor antagonists, of which the most commonly used is clopidogrel, in improving clinical outcomes in patients with ACS and those undergoing percutaneous coronary intervention (PCI) [9–13].

Clopidogrel is a prodrug which, following oral administration, is metabolized to an active metabolite that binds to and irreversibly antagonizes the platelet G_i-linked P2Y₁₂ class of ADP receptors [14]. Clopidogrel is currently the thienopyridine of choice due to its more favourable safety profile compared with the first approved thienopyridine, ticlopidine. However, there are reported limitations of clopidogrel therapy, namely variability in antiplatelet effects and a relatively slow onset of action [15–18].

More recently, a novel thienopyridine P2Y₁₂ inhibitor, prasugrel (CS-747, LY640315), has been identified and profiled [19–23]. Preclinical studies indicate that like clopidogrel, prasugrel is a prodrug that requires metabolic conversion to an active metabolite [19]. Following oral dosing of prasugrel, there is a rapid and potent inhibition of ADP-induced platelet activation and aggregation [19, 22, 23]. These early studies demonstrated that the dose required to achieve a given degree of platelet inhibition or inhibition of thrombus formation in preclinical models was approximately one-tenth and one-hundredth that of clopidogrel and ticlopidine, respectively. The potency, rapid onset of platelet inhibition, and cumulative degree of platelet inhibition with daily dosing of prasugrel were characterized in two early clinical studies evaluating single and multiple daily dosing of prasugrel in healthy volunteers [20, 21]. These early studies, however, were limited by the absence of an active comparator such as clopidogrel.

The objectives of the current multiple-dose study were to determine the pharmacodynamics as measured by inhibition of platelet aggregation, the pharmacokinetics as measured by inactive metabolites, and the safety and tolerability of multiple-dose regimens of prasugrel compared with the standard 75 mg maintenance dose of clopidogrel and placebo in a healthy population in the absence of comedications.

Methods

We conducted a randomized, double-blind, placebo-controlled multiple dose study of prasugrel compared with clopidogrel in healthy subjects. The study was conducted at Inveresk Clinical Research Ltd, Edinburgh, Scotland. The Inveresk Independent Research Ethics committee approved the protocol. Written consent was obtained from each subject and the study was conducted in accordance with the provisions of the Declaration of Helsinki.

Subjects

Subjects were healthy male, nonsmoker volunteers, aged 18–50 years with no clinically important physical findings or abnormalities in laboratory results, including platelet function tests at screening. The screening examination consisted of: medical history, complete physical examination and vital signs, 12-lead electrocardiography (ECG), haematology, coagulation, clinical chemistry and urinalysis, serology for hepatitis and HIV infection, urine screening for drugs of abuse, faecal occult blood examination, bleeding time, von Willibrand factor and arachidonic acid-induced platelet aggregation, and examination for petechiae. All subjects were screened within 14 days prior to randomization. Exclusion criteria included a history of bleeding disorders, reasonable suspicion of vascular malformations, or abnormal coagulation values at screening. No medications other than study drugs were permitted during the study except those deemed necessary by the clinical investigator to treat adverse events. Aspirin and nonsteroidal anti-inflammatory drugs were excluded.

Treatment administered

Prasugrel was manufactured by Ube Industries Ltd. (Tokyo, Japan) and plain tablets containing 5, 10, or 20 mg prasugrel base were formulated by Sankyo Co., Ltd (Tokyo, Japan). Clopidogrel was supplied as the commercially available Plavix® 75 mg tablets. Prasugrel, clopidogrel, and placebo were encapsulated into size 0 capsules without excipients to ensure that the treatments were indistinguishable and that the study remained blinded. Subjects were randomized into three groups of 10 with each group comprised of two subjects receiving placebo, two subjects receiving clopidogrel 75 mg, and two subjects each receiving prasugrel 5, 10, or 20 mg. Drug was administered orally, once daily to each subject. In total, 10 doses were given to each subject. Previous single and 10-day multiple oral dose studies [20, 21] in healthy subjects have shown that prasugrel 10 mg daily was well tolerated and produced a measurable and sustained pharmacodynamic effect on

inhibition of platelet aggregation. Clopidogrel 75 mg is the approved clinical dose for maintenance therapy.

Pharmacodynamic measurements

Prasugrel was assessed for its effects on human platelet function by light transmission aggregometry [24] using a BioData PAP-4 aggregometer. Venous blood samples were collected into one-tenth final volume of 3.8% citrate and platelet-rich and platelet-poor plasma were prepared using differential centrifugation at room temperature. All platelet studies were completed within 3 h of blood collection [24].

Platelet aggregation was measured on day -1, at baseline (i.e. immediately before first dose on day 1), and at 4, 8, and 24 h after dosing on days 1 and 10, at 4 h after dosing on days 3, 5, and 8, and at 48 h after the last dose of study drug on day 10 (i.e. day 12). Platelet aggregation was also assessed on samples drawn on days 13, 14, 17, and 24 if aggregation was inhibited by $\geq 50\%$ at the previous timepoint or mean bleeding time remained prolonged (see following). The maximum platelet aggregation (MPA) response, in percent, achieved in response to ADP ($5 \mu\text{M}$ and $20 \mu\text{M}$), and collagen ($2 \mu\text{g ml}^{-1}$) was recorded during the 4 min following agonist addition. Inhibition of aggregation (IPA) was defined as follows: $\text{IPA} = [1 - (\text{MPA}_t / \text{MPA}_0)] \times 100\%$, where MPA_0 = MPA at baseline and MPA_t = MPA at given timepoint (t).

Bleeding times using the Ivy-Nelson method [25], were determined on day -1, immediately before dosing on days 1, 5, 8, and 10, at 4 and 24 h after dosing on days 1, 5, and 10, just before dosing on day 8, and 48 h after the last dose of study drug on day 10 (i.e. day 12). Bleeding time was also determined on days 13, 14, 17, and 24 if the mean bleeding time was >7 min at the previous timepoint.

Pharmacokinetic measurements

The plasma concentrations of three major prasugrel metabolites, R-95913, R-106583, and R-100932, were measured for evaluation of pharmacokinetics. These are all inactive metabolites, but have been routinely used to determine exposure to prasugrel. Blood (8 ml) was collected from each subject at various time points by a cannula or by repeated venepuncture into lithium heparin tubes. After centrifugation, plasma was stored at -20°C until analysis.

At the time of this study, an assay for the active metabolites of thienopyridines did not exist. However, a validated LC-MS/MS had been developed for quantification of the three major inactive metabolites of prasugrel, including metabolites formed both proximally and

distally to the active metabolite, in human plasma [26]. The prasugrel metabolites were analyzed following solid phase extraction. There was no component present in human plasma that interfered with quantification. The lower limit of quantification for the three metabolites was 1.56 ng ml^{-1} in human plasma.

Safety

Safety assessments performed at various timepoints throughout the study included measurement of vital signs, ECG, haematology, clinical chemistry, coagulation, urinalysis, faecal occult blood, fundoscopy, and examination for petechiae. Adverse events were recorded and monitored throughout the study. Stopping criteria for the study were defined as follows: inhibition of platelet aggregation $>90\%$ to either ADP or collagen with associated prolongation of mean bleeding time of at least 10-times baseline value or >30 min on two successive occasions. Any mean bleeding time at least 10-times baseline value or >30 min on two successive occasions was recorded as an adverse event, even if this prolongation of bleeding time was not associated with any evidence of clinical bleeding. Severity of bleeding events was rated based on blood loss and any requirement for transfusion. Serious adverse events were defined as adverse events which result in death or are life-threatening, require or prolong hospitalization, cause significant disability/incapacity, congenital anomaly/birth defect or are considered serious by the investigator for any other reason.

Statistical analyses

Descriptive statistics generated using SAS (v 6.12) were used to summarize demographics, laboratory parameters, platelet aggregation, bleeding times, and adverse events by dose group.

The pharmacodynamic endpoints for the statistical analysis were platelet aggregation response for each agonist over 4, 8, and 24 h separately and for days 1 and 10 separately. These endpoints were analyzed using one-way analysis of variance (ANOVA) techniques, including a term for treatment. Mean bleeding times at 4 h post-dose were compared with placebo using Dunnett's multiple comparison. Due to the exploratory nature of these analyses, no adjustment for multiple comparisons was performed.

Non-compartmental pharmacokinetic parameters were estimated for the metabolites using WinNonlin pharmacokinetic software (version 1.5, Scientific Consulting Inc., Cary, NC). Summary statistics for the parameter estimates of $\text{AUC}_{0-24 \text{ h}}$, the area under the plasma drug concentration vs. time curve from time zero

to time 24 h, C_{max} , maximum concentration of drug in plasma measured in each subject after dosing for each dose group and t_{max} , the time at which C_{max} is apparent, at each dose on days 1, 5, and 10 were obtained.

Results

Subjects

Thirty-one healthy male subjects were enrolled in the study. One subject withdrew consent on day 8 and was replaced. A total of 30 subjects completed the study. One subject received only nine of the planned 10 doses and day 10 assessments were performed on day 9. All 31 subjects were included in the statistical analysis. All subjects were Caucasian. Their mean age was 31.5 ± 9.8 years (range 18–50 years) and their mean weight was 79.3 ± 8.0 kg (range 62.6–93.4 kg).

Platelet aggregation

Platelet inhibition increased over time reaching steady-state after approximately 3 days in the prasugrel 10 mg and 20 mg dose groups (Figure 1). Steady-state inhibition of platelet aggregation with clopidogrel 75 mg and prasugrel 5 mg was reached after approximately 5 days of drug administration. At day 10, 24 h postdose, with $5 \mu\text{M}$ ADP, inhibition of platelet aggregation achieved with all doses of prasugrel was higher than the inhibition observed with clopidogrel 75 mg (prasugrel 20 mg, 77.2%; prasugrel 10 mg, 70.5%; prasugrel 5 mg, 52.7% vs. clopidogrel 75 mg, 36.5%). Inhibition of platelet aggregation at this timepoint with all doses of prasugrel was significantly higher than placebo (prasugrel 5 mg, $P = 0.0002$; prasugrel 10 and 20 mg, $P < 0.0001$), as was inhibition of platelet aggregation with clopidogrel 75 mg ($P = 0.02$). With $20 \mu\text{M}$ ADP as agonist, inhibition of platelet aggregation was significantly higher than placebo only in the prasugrel groups (placebo, 9.2%; prasugrel, 20 mg 68.3%, $P < 0.0001$; prasugrel 10 mg, 58.2%, $P < 0.0001$; prasugrel 5 mg, 39.2%, $P = 0.001$; clopidogrel 75 mg, 15.7%, $P = 0.78$ vs. placebo). We noted, but could not find an explanation for, the apparent increase in IPA in the placebo group on day 10. Lower levels of inhibition of platelet aggregation were observed with collagen ($2 \mu\text{g ml}^{-1}$) as the agonist on day 10 24 h postdose and inhibition of platelet aggregation was significantly higher than placebo only with prasugrel 10 mg (placebo, 8.3%; prasugrel 20 mg, 23.0%, $P = 0.14$; prasugrel 10 mg, 30.8%, $P = 0.01$; clopidogrel, 7.3%, $P = 0.99$ vs. placebo).

Figure 2 illustrates the consistency of response over time obtained with prasugrel 10 mg. In all subjects receiving prasugrel 10 mg, the maximum inhibition of platelet aggregation at the end of the study (24 h after

Figure 1

Inhibition of ADP-induced platelet aggregation with daily prasugrel compared with daily clopidogrel and placebo. Mean inhibition of platelet aggregation at selected timepoints induced by $5 \mu\text{M}$ ADP (Panel A) and $20 \mu\text{M}$ ADP (Panel B) is illustrated. Solid circles represent placebo; open circles, 5 mg prasugrel; closed squares, 10 mg prasugrel; open squares, 20 mg prasugrel; closed triangles, 75 mg clopidogrel. Values are mean $\pm$ SEM, $n = 6$ for all groups

administration of last dose) was at least 53% (range 53%–86%) with $5 \mu\text{M}$ ADP as the agonist and with $20 \mu\text{M}$ ADP as agonist was at least 42% (range 42%–71%). Similar consistency was observed with prasugrel 20 mg (data not shown). In the clopidogrel 75 mg group with $5 \mu\text{M}$ ADP as agonist, three of six subjects (subjects 9, 11, and 12) had little or widely variable inhibition of platelet aggregation throughout the 10 days of multiple dosing and at 24 h after administration of last dose (range, 0%–58%) (Figure 3). With $20 \mu\text{M}$ ADP as agonist, inhibition of platelet aggregation ranged from

Figure 2

Individual % inhibition of ADP-induced platelet aggregation during the study for each subject receiving prasugrel 10 mg. Platelet aggregation was induced by 5 μ M (solid circles) or 20 μ M (ADP, open circles)

Figure 3

Individual % inhibition of ADP-induced platelet aggregation during the study for each subject receiving clopidogrel 75 mg. Platelet aggregation was induced by 5 μ M (solid circles) or 20 μ M (ADP, open circles)

0%–38% 24 h after administration of the last dose of clopidogrel. Inhibition of platelet aggregation in the placebo group at the end of the study ranged from 0%–34% with 5 μ M ADP as the agonist and 0%–25% with 20 μ M ADP as the agonist. Consequently, clopidogrel subjects 9, 11, and 12 could not readily be distinguished from subjects receiving placebo.

Bleeding time

The mean bleeding times at 4 h postdose for each treatment group on days 1, 5, and 10 are summarized in Table 1. There was a significant increase in bleeding time on days 5 and 10 for both prasugrel 10 and 20 mg compared with placebo. There was no significant increase in bleeding time with clopidogrel administration. While three bleeding time prolongations in each of the 10 mg and 20 mg prasugrel groups were categorized as adverse events, these did not trigger discontinuation of the study drug, severe or serious bleeding episodes, or the need for medical intervention.

Pharmacokinetics

Pharmacokinetic parameters for the three prasugrel inactive metabolites, R-95913, R-100932, and R-106583 are summarized in Table 2. The mean C_{max} of the prasugrel metabolites on both day 1 and day 10 increased almost proportionally as a function of dose, as did the $AUC_{0-24\text{ h}}$.

Adverse events

A total of 59 adverse events in 20 subjects occurred after dosing during the study, of which 44 (35 excluding repetitions of the same adverse event in the same subject) were considered possibly or probably related to one of the study drugs. All of the events were considered mild to moderate in severity by the clinical investigator. None of these events was considered serious or resulted in discontinuation of study drug and there were no significant differences in frequency of adverse events between treatment groups. The number of subjects with adverse events considered by the investigator as related to administration of study drug were as follows: placebo ($n = 3$), prasugrel 5 mg ($n = 2$), prasugrel 10 mg ($n = 5$), prasugrel 20 mg ($n = 4$), and clopidogrel ($n = 1$). Adverse events reported more than once and considered by the investigator as related to administration of study drug were headache ($n = 3$) in the prasugrel 10 mg group, alanine aminotransferase (ALT) increased ($n = 2$) after prasugrel 20 mg, and positive faecal occult blood after placebo ($n = 3$) and prasugrel 20 mg ($n = 3$). Transient elevations in liver enzymes, ALT or aspartate aminotransferase (AST), were observed in three subjects

Table 1
Mean bleeding times at 4 h postdose in each treatment group

Time after prasugrel administration	Treatment group					
	Placebo ($n = 6$)	Prasugrel 5 mg ($n = 6$)	Prasugrel 10 mg ($n = 6$)	Prasugrel 20 mg ($n = 6$)	Prasugrel BT ratio vs. placebo	Clopidogrel BT ratio vs. placebo
Day 1	144 $\pm$ 13	181 $\pm$ 21	217 $\pm$ 47	581 $\pm$ 308	1.5	1.3
Day 5	223 $\pm$ 18	351 $\pm$ 111	1053 $\pm$ 391	1515 $\pm$ 273	4.7	1.4
Day 10	201 $\pm$ 38	288 $\pm$ 50	706 $\pm$ 252	728 $\pm$ 162	3.5	1.4
					<i>P</i> value	<i>P</i> value
					0.98	0.98
					0.98	0.98
					0.04	0.98
					0.05	0.98
					0.11	0.98
					0.001	0.98
					4.0	1.3
					6.8	1.4
					3.6	1.4
					186 $\pm$ 22	1.3
					302 $\pm$ 70	1.4
					283 $\pm$ 56	1.4

Bleeding times in seconds are expressed as mean $\pm$ SEM. *P* values are for prasugrel or clopidogrel group comparison with placebo using Dunnett's test.

Table 2

Pharmacokinetic parameters of prasugrel metabolites

Study day	Parameter	Prasugrel dose (mg)		
		5 (n = 6)	10 (n = 6)	20 (n = 6)
R-95913				
Day 1	AUC _{0–24 h} (ng ml ^{–1} h)	22.4 ± 9.2	47.3 ± 11.2	108.4 ± 37.1
	C _{max} (ng ml ^{–1})	10.7 ± 3.3	18.2 ± 6.9	39.7 ± 13.4
	t _{max} (h)	1.8 ± 0.4	2.0 ± 1.1	1.7 ± 0.5
Day 10	AUC _{0–24 h} (ng ml ^{–1} h)	31.9 ± 8.0	73.0 ± 18.2	168.4 ± 56.5
	C _{max} (ng ml ^{–1})	14.2 ± 5.2	25.1 ± 9.7	43.9 ± 19.6
	t _{max} (h)	1.7 ± 0.5	1.8 ± 1.2	1.8 ± 0.4
R-106583				
Day 1	AUC _{0–24 h} (ng ml ^{–1} h)	253.5 ± 74.3	415.8 ± 149.5	782.0 ± 169.0
	C _{max} (ng ml ^{–1})	34.6 ± 11.0	61.0 ± 22.4	120.7 ± 27.6
	t _{max} (h)	2.7 ± 1.0	2.7 ± 1.0	2.3 ± 0.8
Day 10	AUC _{0–24 h} (ng ml ^{–1} h)	312.7 ± 85.4	487.3 ± 218.0	729.3 ± 200.6
	C _{max} (ng ml ^{–1})	45.2 ± 20.0	61.3 ± 29.8	92.2 ± 27.0
	t _{max} (h)	1.8 ± 0.4	2.5 ± 1.2	2.3 ± 0.8
R-100932				
Day 1	AUC _{0–24 h} (ng ml ^{–1} h)	57.6 ± 19.1	81.1 ± 11.2	154.2 ± 20.9
	C _{max} (ng ml ^{–1})	9.0 ± 2.5	15.3 ± 4.4	32.3 ± 5.5
	t _{max} (h)	2.0 ± 0.0	2.2 ± 1.0	1.8 ± 0.4
Day 10	AUC _{0–24 h} (ng ml ^{–1} h)	66.1 ± 12.0	99.3 ± 20.9	159.3 ± 23.5
	C _{max} (ng ml ^{–1})	10.4 ± 15.8	17.0 ± 5.2	26.3 ± 5.4
	t _{max} (h)	1.8 ± 0.4	2.3 ± 1.4	2.3 ± 0.8

All data are expressed as mean ± SEM. AUC_{0–24 h} the area under the plasma drug concentration vs. time curve from time zero to 24h after dosing; C_{max} maximum concentration of drug in plasma measured in subject after dosing; t_{max} the time at which C_{max} was apparent.

receiving prasugrel and one subject receiving clopidogrel. Stools positive for faecal occult blood were observed in all treatment groups except prasugrel 10 mg. The incidence of positive faecal occult blood tests was identical in the prasugrel 20 mg and the placebo-treated groups, and lower in the other three treatment groups. There were no clinically significant changes in vital signs, ECGs, haematology, urinalysis, physical examination, fundoscopy, or presence of petechiae for any subject during the course of the study.

Discussion

While a previous study [21] described the platelet inhibitory effects and pharmacokinetics of multiple doses of prasugrel, the present study is the first to include a direct comparison of the thienopyridine antiplatelet agent, prasugrel (CS-747, LY640315) with clopidogrel in healthy volunteers. The current results indicate that dose-dependent inhibition of ADP-induced platelet aggregation during daily dosing was significantly greater with prasugrel 10 and 20 mg compared with both placebo and

clopidogrel 75 mg. Steady-state inhibition of aggregation by prasugrel 10 and 20 mg was achieved more quickly than with clopidogrel 75 mg. Prasugrel 5, 10, or 20 mg daily for 10 days was safe and well-tolerated based on the safety parameters measured in the study.

Repetitive dosing over a 10-day period with ascending doses of prasugrel resulted in higher levels of platelet inhibition compared with clopidogrel. The greater inhibition of platelet aggregation observed with prasugrel 10 and 20 mg is consistent with the modest and dose-dependent prolongation in mean bleeding time observed in those dose groups. The prolongation of bleeding time was greater with prasugrel 10 and 20 mg compared with clopidogrel 75 mg; however, the increase in bleeding time in the prasugrel groups did not result in clinically evident bleeding events or study drug discontinuation. A prolongation of the bleeding time of approximately two times baseline after 11 days of clopidogrel 75 mg was previously reported in healthy subjects [27] compared with the 1.3-fold prolongation in bleeding time at day 10 with clopidogrel 75 mg in the

current study. The observed 3.5-times prolongation of bleeding time with prasugrel 10 or 20 mg after 10 days of dosing in this study is higher compared with the 1.5-times increase in bleeding time previously reported with administration of 300 mg aspirin [28].

Consistent with a previous multiple oral dose study of prasugrel, inhibition of platelet aggregation by prasugrel 10 and 20 mg reached steady-state by days 2–4 of daily dosing and was maintained throughout the remainder of the dosing period [21, 23]. In contrast, clopidogrel 75 mg did not reach steady-state until days 5–6, consistent with observations in an earlier repeated-dose study of clopidogrel in healthy subjects [27]. In the present study, prasugrel was at least 10-times more potent than clopidogrel supporting previous preclinical results [19, 22, 23]. With 5 μ M ADP as agonist, a mean inhibition of platelet aggregation of approximately 37% was observed with clopidogrel 75 mg 24 h after the last dose compared with 71% inhibition with prasugrel 10 mg. Slightly lower levels of inhibition of aggregation were found with the higher agonist dose of 20 μ M ADP. Inhibition of aggregation observed with clopidogrel in this study is consistent with previous results in healthy subjects [27].

In this first direct clinical comparison of prasugrel with clopidogrel, consistent inhibition of platelet aggregation with prasugrel 10 and 20 mg was observed in all subjects in this study while clopidogrel demonstrated low or variable inhibition of platelet aggregation (Figures 2 and 3). The range of inhibition of aggregation by clopidogrel 75 mg overlapped, in part, with that observed in the placebo group. Little or widely variable inhibition of platelet aggregation in three of six clopidogrel subjects was observed. This is consistent with previously reported results observed with clopidogrel 75 mg, where 25% to 30% of patients typically have poor inhibition of platelet aggregation when studied under similar conditions [16–18, 29]. It should be noted that the sample size in the current study is small and results could differ in a larger sample size or in a patient population, particularly if co-administered with aspirin.

For all inactive metabolites of prasugrel measured, the maximum plasma concentration increased almost proportionally as a function of dose and the time to maximum plasma concentration was not significantly affected by the dose of prasugrel. No significant accumulation was apparent for any metabolites during multiple doses for 10 days.

The results of this study comparing prasugrel and clopidogrel in healthy subjects indicated that prasugrel at daily doses of 20 mg or less for 10 days was well

tolerated and provided cumulative high levels of inhibition of platelet aggregation after 3 days of oral dosing. The results for prasugrel are in agreement with previous studies of prasugrel [20, 21] in healthy volunteers, but which did not include a clopidogrel comparison. Inhibition of platelet aggregation was greater with 10 and 20 mg prasugrel compared with clopidogrel 75 mg and the consistency of response to prasugrel was better than that observed with clopidogrel. In subsequent studies, levels of the active metabolites of clopidogrel and prasugrel have been measured and indicate that prasugrel administration results in substantially greater exposure to its active metabolite than does clopidogrel (data on file, Eli Lilly and Company). These differences are felt, in a large part, to account for the marked differences in potency between prasugrel and clopidogrel. More recently the safety and antiplatelet activity of prasugrel has been studied in patients with coronary artery disease [30, 31]. Results from all of these studies, in part, enabled the selection of a maintenance dose of prasugrel (10 mg) for the ongoing TIMI 38 phase 3 trial comparing prasugrel with clopidogrel in ACS patients undergoing PCI [TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)]. This trial will determine if higher and more consistent platelet inhibition with prasugrel results in improved clinical outcome.

Financial support and potential conflict of interest

The study was supported by Sankyo Co., Ltd, Tokyo, Japan. Drs Asai, Naganuma, and Hirota and Ms Matsushima are employees of Sankyo Co., Ltd, Tokyo, Japan. Drs Jakubowski, Brandt, and Winters are employees and stockholders of Eli Lilly and Company. Sankyo Co., Ltd and Eli Lilly and Company are currently codeveloping prasugrel for potential clinical use. Dr Freestone is an employee of Inveresk Clinical Research Ltd. (now known as Charles River Laboratories).

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