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Platelet inhibitory activity, tolerability, and safety of vicagrel, a novel thienopyridine P2Y12 inhibitor

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Abstract

Vicagrel is a new antiplatelet pro-drug based on clopidogrel sulfur lactone metabolites. The purpose of the study was to evaluate the safety, tolerability, and pharmacodynamics (PD) of vicagrel in healthy Chinese subjects.

This study was designed as a single-center, randomized, double-blind, placebo-controlled, single oral ascending dose study. Fifty nine subjects were assigned to 6 vicagrel dose cohorts (5, 10, 20, 40, 60, and 75 mg), and 8 subjects were assigned to 75 mg clopidogrel. Within each vicagrel dose cohort, the 10 subjects (9 in the 75 mg cohort) were randomized 4:1 to receive vicagrel or placebo. Platelet function was assessed using VerifyNow™ P2Y12. ΔP2Y12 reaction units (ΔPRU) and percent inhibition platelet aggregation (%IPA) were used to evaluate the PD of vicagrel.

Although the number of adverse events (AEs) increased with vicagrel dose, none were considered serious, suggesting that vicagrel is safe and well-tolerated. The ΔPRU and %IPA patterns suggest that inhibition of ADP-induced platelet aggregation increased in a dose-dependent manner across the 10 to 40 mg dose range. The inhibitory effect was nearly complete at 4 hours (mean %IPA 87.9%–93.0%, mean ΔPRU 206.6–240.0) for doses of 40 to 75 mg of vicagrel. In contrast, for 5 mg vicagrel and 75 mg clopidogrel, there were no measurable effects on platelet aggregation throughout the study.

The results suggest that vicagrel at 40 to 75 mg inhibits ADP-induced platelet aggregation, with a fast onset of action and significantly greater potency than clopidogrel. These findings indicate that vicagrel may be a highly effective and well-tolerated antiplatelet agent.

Abbreviations: %IPA = percent inhibition platelet aggregation, ΔPRU = ΔP2Y12 reaction units, AADAC = arylacetamide deacetylase, ACS = acute coronary syndrome, AEs = adverse events, APTT = activated partial thromboplastin time, CES2 = carboxylesterase-2, CRF = case report form, CTCAE = Common Terminology Criteria for Adverse Events, CVA = cerebral vascular accident, HCT = hematocrit, PCI = percutaneous coronary intervention, PD = pharmacodynamics, PLT = platelet count, PT = prothrombin time.

Keywords: healthy Chinese subjects, pharmacodynamics, platelet aggregation, vicagrel

1. Introduction

In China, approximately 20 million people live with coronary heart disease, which is now the leading cause of death.[1–3] The standard treatment for patients with acute coronary syndrome includes dual-antiplatelet therapy, usually aspirin and a drug of the thienopyridine class (P2Y12 inhibitor), which has been proven to be efficacious in reducing the rate of recurrent cardiac events.[4]

Clopidogrel, the most commonly prescribed thienopyridine, is a pro-drug that requires metabolism by hepatic cytochrome P450 (CYP) enzymes to form active thiol metabolites. The main enzyme for the metabolism of clopidogrel into 2-oxo-clopidogrel is CYP2C19 (44.9%), but CYP1A2 (35.8%) and CYP2B6 (19.4%) also contribute to this metabolism, while 2-oxo-clopidogrel is metabolized into the active metabolite by the action of CYP2C19 (20.6%), CYP2C9 (6.8%), CYP2B6 (32.9%), and CYP3A4 (39.8%).[5,6] Kazui et al. showed that CYP2C19 contributes substantially to both oxidative reactions and that CYP3A4 contributes substantially to the second step.[6] Since CYP2C9 is involved in both reactions, any changes in its activity will have significant impacts on the formation of the active metabolite and hence, on the response to treatment.[5] The active metabolite binds to and irreversibly antagonizes the P2Y12 class platelet ADP receptor.[7] Nevertheless, non-responsiveness or poor responsiveness to clopidogrel (i.e., clopidogrel resistance)

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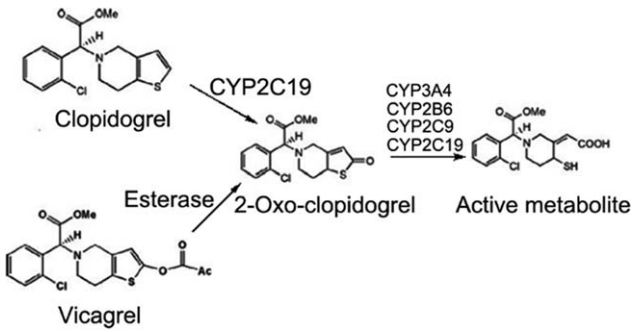

Figure 1. Metabolic activation of clopidogrel and vicagrel. Clopidogrel and vicagrel share the same intermediate (2-oxo-clopidogrel) and the same active metabolite (active clopidogrel metabolite), but they differ in the first metabolic step. Clopidogrel is metabolized to 2-oxo-clopidogrel through CYP2C19, whereas vicagrel is hydrolyzed into 2-oxo-clopidogrel via carboxylesterase-2 (CES2) or arylacetamide deacetylase (AADAC).

occurs in up to 30% of Caucasians, 40% of individuals of African origin, and 55% of Asians, and is accompanied by lower concentrations of the active metabolite of clopidogrel, lower inhibition of platelets, and higher risk of death and myocardial event.[8,9] In 2010, the FDA released a black-box warning on clopidogrel to make patients and healthcare professionals aware that poor metabolizers of CYP2C19 are at high risk of treatment failure.

On the basis of this understanding, a novel ester pro-drug, vicagrel ((S)-methyl 2-(2-acetoxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(2-chlorophenyl)-acetate) has been developed.[10] Vicagrel is hydrolyzed into its thiolactone intermediate, 2-oxo-clopidogrel, via carboxylesterase-2 (CES2) or arylacetamide deacetylase (AADAC) instead of CYPs. As shown in Figure 1, vicagrel shares the same metabolites and mechanism as clopidogrel (as presented above), except that the first step is not catalyzed by CYP2C19, circumventing the clopidogrel resistance observed in patients with low CYP2C19 activity. Therefore, the use of vicagrel may overcome clopidogrel resistance in poor CYP2C19 metabolizers by circumventing the CYP metabolic steps.

Preclinical studies have shown that vicagrel is extensively and rapidly converted to 2-oxo-clopidogrel and active metabolites, at about five-fold higher conversion rates than clopidogrel at equal molar doses in rats and dogs.[11] This suggests that vicagrel could be a promising agent to prevent platelet aggregation and overcome clopidogrel resistance and high inter-individual response variability due to CYP2C19 polymorphism.

Considering the novelty of vicagrel, the present clinical trial aimed to evaluate the safety, tolerability, and pharmacodynamics (PD) of vicagrel in healthy Chinese subjects. The findings should provide a foundation for future clinical trials to evaluate the clinical use of vicagrel. The pharmacokinetics and pharmacokinetic/pharmacodynamic relationship analyses of the same study population have been reported by Liu et al.[12]

2. Material and methods

2.1. Study design

This study was designed as a single-center, randomized, double-blind, placebo-controlled, single oral ascending dose study. According to the techniques for investigating the clinical pharmacokinetics of chemical drugs, 8 to 12 patients were required in each dose group.[13] The study protocol was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University (No 2015–38). Informed consent was obtained from all participants.

2.2. Study population

All the participants were recruited from the Zhongshan Hospital, Fudan University, in 2015. The inclusion criteria were:

1. healthy individuals (either males or females), 18 to 45 years of age;
2. body mass index (BMI) 18 to 24 kg/m^2; ≥50 kg for male subjects; ≥45 kg for female subjects;
3. without history of vital organ disorders; physical examinations, vital signs, laboratory examinations, and other related examinations all showed normal results, or showed abnormal results that were with no clinical significance;
4. the males subjects had to agree to use reliable contraceptive methods and not donate sperms from screening to 3 months after study completion; females had to meet the following items: blood pregnancy test at screening showed negative results; not lactating; with no fertility plan from 1 month before participating to 4 weeks after study completion, and agreed to use reliable contraceptive methods (tubal ligation, hysterectomy, and use contraceptive device (such as condom and/or vaginal septum) in addition to abstinence or intrauterine device);
5. anterior and lateral thoracic X-ray images obtained within 28 days before the trial and showing normal images;
6. volunteered to participate in this study and signed the informed consent form; and
7. willing to and could abide by all the study protocols, including visiting, treatments, laboratory examinations, and other procedures.

The exclusion criteria were:

1. history of abnormal bleeding (such as prolonged bleeding time after tooth extraction);
2. family history of blood coagulation disorders or hemorrhagic disorders (such as hemophilia), of symptoms such as hematemesis, melena, severe or repeated epistaxis, hemoptysis, evident hematuresis, or intracranial hemorrhage, or were suspected with vascular malformation such as arterial aneurysm or early onset cerebral stroke (cerebral vascular accident (CVA) <65 years of age);
3. severe allergy, non-allergic drug reactions, or history of allergy to various drugs; or were known or possibly to be allergic to the class of drugs to be investigated, or with high sensitivity to clopidogrel;
4. dyspepsia, esophageal reflux, gastrorrhagia, or peptic ulcer currently or within the past 6 months, with at least 1 heartburn every week, or received surgical treatments (such as cholecystectomy) that could affect drug absorption;
5. participated in any clinical trials or intake of any known liver enzyme inducers/inhibitors within 3 months before this study;
6. received major operations within 3 months before this study, or planned to receive operation during the study or within 14 days after study completion;
7. history of blood loss or blood donation of >300 ml within the past 90 days (since the day before drug administration);
8. used aspirin, NSAIDs, or other drugs that could affect blood coagulation within 2 weeks before the study;

9. history of grapefruit juice or other diets that could affect the functions of hepatic metabolic enzymes within 1 week before the study, performed strenuous exercises within 48 hours before drug administration, or with other factors that could affect the absorption, distribution, metabolism, or excretion of the drugs;
10. used any drugs, including non-prescription drugs and/or replacement drugs (such as herbal cuisine, Chinese herbal medicine, hemostatic, or blood circulation promoting plants, or supplementary health care products) within 1 week before the study, or use hormonal birth control;
11. petechiae and/or ecchymoses on the skin;
12. prothrombin time (PT) and/or activated partial thromboplastin time (APTT) higher than the upper limit of the normal range;
13. hematocrit (HCT) or platelet count (PLT) beyond the normal range;
14. ALT, AST, or TBIL higher the upper limit of the normal range;
15. history of psychoactive substance abuse, or with drug abuse in the screening/baseline phase, and positive urine drug screening showed;
16. history of smoking (consuming over 5 cigarettes or equal tobacco every day);
17. history of regular alcohol drinking; >7 drinks/week for females or >14 drinks/week for males [1 drink = 5 ounces (150 mL) of wine = 12 ounces (360 ml) of beer = 1.5 ounces (45 ml) of spirits]; or positive breathalyzer test within 24 hours before the drug administration or within the screening phase;
18. sitting systolic blood pressure >140 mm Hg or <90 mm Hg, diastolic blood pressure >90 mm Hg or <60 mm Hg, or pulse <50 beats/minute or >100 beats/minute during the screening;
19. 12-lead ECG in supine position during the screening showed QtcB >450 ms;
20. antibody to human immunodeficiency virus antibody (HIV-Ab), syphilis serology examination, hepatitis B virus surface antigen (HBsAg), or antibody to hepatitis C virus (HCV-Ab) was positive;
21. partners refused to use effective contraception methods from screening to 3 months after study completion; or
22. any subject deemed unfit for participation by the investigators.

2.3. Randomization and blinding

The serial numbers of the drugs for the subjects were provided by an independent clinical research organization, and the randomization table was generated by computer using statistical software. In this study, 60 serial numbers were generated, with 10 numbers for each dose group. Stratified randomization by sex was conducted. The drugs were packed and numbered by individuals irrelevant to this study. The emergency envelopes were also generated with the treatment codes and were delivered to the investigators along with the drugs, for emergent unblinding.

2.4. Drug administration

Specification of vicagrel tablets: 2.5 mg/10 mg; batch number: 150301; effective duration: 2 years (provisional). Specification of the placebo: 25 mg; batch number: 150304; effective duration: 2 years (provisional). Both the vicagrel tablets and placebo were provided by Jiangsu Vcare Pharmatech Co., Ltd. The appearance of the vicagrel and vicagrel placebo was the same for each dose group, but the appearance of clopidogrel was different. The patients receiving clopidogrel were grouped separately, and no clopidogrel placebo was used. No patient received the 2 drugs at the same time. Each patient was isolated behind curtains when taking the drug.

After eligibility confirmation at screening, 59 subjects were assigned to 6 different vicagrel dose cohorts (5, 10, 20, 40, 60, and 75 mg). Within each dose cohort, 10 subjects (9 subjects in the 75 mg cohort) were randomized to receive either active or matching placebo treatment with a ratio of 4:1, based on randomization provided by an independent statistician. Each subject was assigned to only 1 dose of treatment. The clopidogrel cohort was open-label and included 8 subjects randomly assigned to 75 mg of clopidogrel.

Figure 2 shows the study timeline. Subjects were screened between day -28 and day -7 and admitted to the clinic on day -2. Each subject was fasted overnight (at least 10 hours) on day -1 (baseline) before taking the morning dose of the drug or placebo with 240 ml of water on day 1. Additional water intake was not allowed for 1 hour before and after dose administration. All subjects were served standardized meals during this study. The first meal was served 4 hours after dose administration on the morning of day 1. The subjects were discharged on day 4.

2.5. Safety assessment

Safety evaluation was conducted by the investigator throughout the course of the study and included physical examination, vital signs (e.g., blood pressure, heart rate, respiratory rate, and ear temperature), 12-lead ECG, clinical laboratory tests (e.g., hematology, serum biochemistry, and urinalysis), coagulation system measurements, adverse events (AEs), and a global assessment of tolerability.

Vital signs were assessed at screening, prior to dosing (day -1), and after dosing (day 1 to day 4). Twelve-lead ECGs were recorded at screening, and on day -1 to day 4. Hematology, serum biochemistry, and urinalysis were performed at screening, on day -1, and on day 4. Coagulation was evaluated at screening, on day -1, and on day 1 to day 4. AEs were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. The adverse events were classified according to the following criteria: grade 1 = mild; grade 2 = moderate; grade 3 = severe, grade 4 = life-threatening, and grade 5 = death.

All adverse events or other symptoms and signs after drug administration were recorded in the original medical record and case report form (CRF), irrespective of the relationships with the drugs. All adverse events that occurred within 72 hours after drug administration were recorded.

2.6. Pharmacodynamic assessment

The VerifyNow^{TM} P2Y12 (Accumetrics, San Diego, CA, USA) assay is a whole-blood, point-of-care, light transmission-based optical detection assay that measures platelet-induced aggregation in a single-use disposable cartridge containing fibrinogen-coated beads.[14] The instrument automatically reports P2Y12 reaction units (PRU) and percent inhibition of platelet aggregation (%IPA). PRU values are indicative of residual platelet

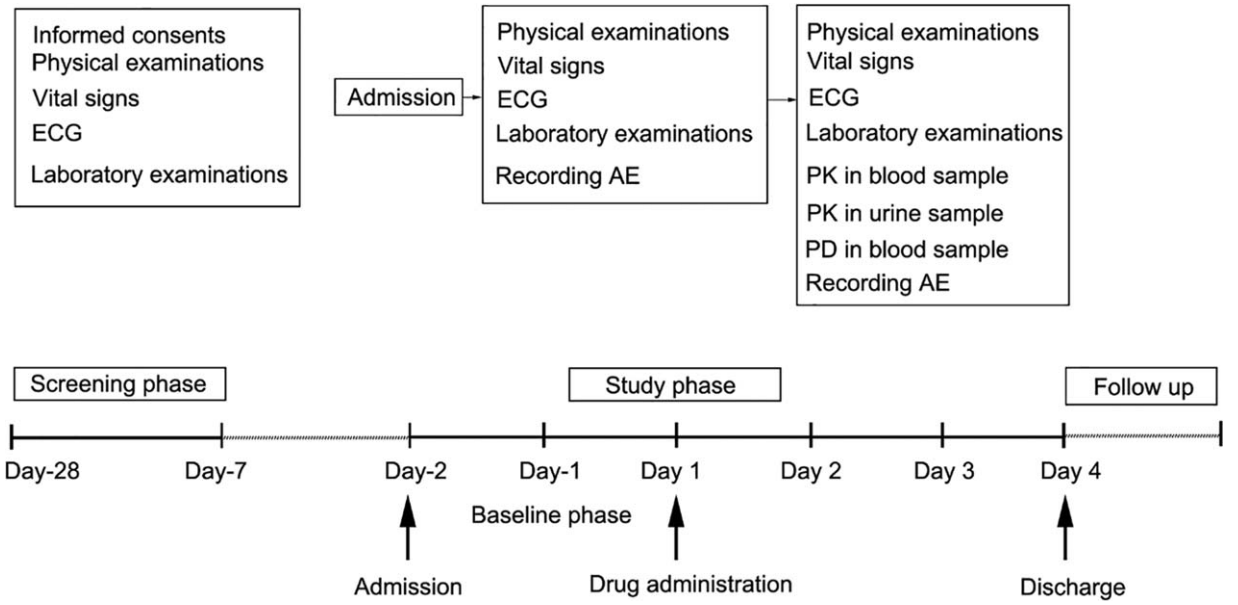

Figure 2. Schema of the study process.

reactivity. %IPA indicates the extent of P2Y12 blockade by P2Y12 inhibitors, using the post-dosing BASE ($BASE_t$) and PRU (PRU_t). We also assessed ΔP2Y12 reaction units (ΔPRU), using the baseline PRU (PRU_b: predose) and PRU_t to measure the pharmacodynamics characteristics:

$$\%\,\mathrm{IPA} = \frac{\mathrm{BASEt} - \mathrm{PRUt}}{\mathrm{BASEt}} \times 100\%,$$

$\Delta\mathrm{PRU} = \mathrm{PRU_b} - \mathrm{PRU_t}$.

Blood samples of approximately 2 ml were collected into citrate tubes for the assessment of platelet aggregation using VN-P2Y12. Samples were collected on day -1, and 0.5, 1, 2, 4, 8, and 24 hours post-dose. Of note, the VerifyNow^{TM} device is associated with a coefficient of variation of <8%.[15] Therefore, for values in the low range, it is possible that the PRU value after administration was higher than the baseline value, resulting in a negative ΔPRU.

2.7. Statistical analysis

All the analyses were conducted using SAS 9.2 (SAS Institute, Cary, NY, USA). Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as means ± standard deviation. Non-normally distributed continuous data are presented as medians (range). Categorical data were expressed as frequencies (percentage).

3. Results

3.1. Subject enrollment and demographics

Sixty seven healthy Chinese subjects (34 males and 33 females) were enrolled in this study. Eight subjects were assigned to the clopidogrel group. The other 59 subjects were administered single doses of 5, 10, 20, 40, 60, or 75 mg of vicagrel or placebo (8 subjects at each dose and 2 placebo subjects per group). One subject in the 75 mg group was excluded prior to drug administration. The information of the subjects was checked again according to the eligibility criteria on the day before drug administration; the blood routine examinations showed that the HCT of this subject on day -1 was 51.1%, which was beyond the normal range; the white blood cell count was 11.34×10^9, which was also beyond the normal range; the investigators believed that the abnormalities were with clinical significance. There were 9 subjects (including 2 placebo subjects) in the 75 mg group. All reported demographics and baseline characteristics were not different among the treatment groups (Table 1).

3.2. Vicagrel safety and tolerability

The assessment of vicagrel safety and tolerability suggests that single oral doses of 5, 10, 20, 40, 60, and 75 mg were safe and fairly well tolerated in healthy Chinese volunteers. Though there were AEs, none was considered serious, and no subjects withdrew from the study due to AEs. The AEs following vicagrel or clopidogrel administration are summarized in Table 2. Among the 49 subjects who were administered vicagrel, 17 subjects (36.2%) reported a total of 25 AEs following the administration of 5 mg (n = 1/8), 20 mg (n = 2/8), 40 mg (n = 4/8), 60 mg (n = 5/8), or 75 mg (n = 5/7) of vicagrel. Furthermore, among the 8 subjects who were administered clopidogrel, 1 subject (n = 1/8) reported 1 AE. No AEs were reported in the placebo group. The placebo group and the 47 subjects who were administered vicagrel showed a statistically significant difference in the number of AEs (P = 0.014). Compared with the placebo group, the clopidogrel group and lower doses of vicagrel (5, 10, and 20 mg groups) showed similar percentages of AEs ($P > .05$ for 5, mg, and 20 mg vicagrel vs placebo), while the higher dose vicagrel (40, 60, and 75 mg) groups had higher frequencies of AEs ($P < .05$ for 40, 60, and 75 vicagrel vs placebo). One of the AE's (prolonged PT in the 60 mg group) was considered by the investigator to be of moderate intensity. The other 23 AEs were of mild intensity. No serious AEs were reported (Table 3).

Table 1

Demographic and baseline characteristics of the subjects.

	Vicagrel							Clopidogrel	Placebo
Index	5 mg (N = 8)	10 mg (N = 8)	20 mg (N = 8)	40 mg (N = 8)	60 mg (N = 8)	75 mg (N = 7)	Total (N = 47)	75 mg (N = 8)	(N = 12)
Age, Years	25.6 ± 4.5	27.7 ± 3.0	24.1 ± 3.8	24.1 ± 1.9	25.6 ± 2.0	24.6 ± 2.7	25.1 ± 3.2	24.0 ± 2.5	24.0 ± 3.3
Sex, n (%)									
Male	4 (50%)	4 (50%)	5 (62.5%)	4 (50%)	4 (50%)	3 (43%)	24 (51%)	4 (50%)	6 (50%)
Female	4 (50%)	4 (50%)	3 (37.5%)	4 (50%)	4 (50%)	4 (57%)	23 (49%)	4 (50%)	6 (50%)
BMI, kg/m^2	21.7 ± 1.9	20.6 ± 1.5	22.0 ± 1.5	21.6 ± 1.8	22.5 ± 1.8	22. 6 ± 1.9	21.8 ± 1.7	21.4 ± 1.6	21.5 ± 2.1

N, number of subjects.
BMI = body mass index, SD = standard deviation.

Table 2

Adverse events in the different dose groups of vicagrel, clopidogrel group, and placebo group.

	Vicagrel							Clopidogrel	
	5 mg (N = 8)	10 mg (N = 8)	20 mg (N = 8)	40 mg (N = 8)	60 mg (N = 8)	75 mg (N = 7)	Total (N = 47)	75 mg (N = 8)	Placebo (N = 12)
With at least 1 AE	1 (12.5%)	0	2 (25.0%)	4 (50.0%)	5 (62.5%)	5 (71.4%)	17 (36.1%)	1 (12.5%)	0
Examination results	0	0	1 (12.5%)	1 (12.5%)	4 (50.0%)	5 (71.4%)	11 (23.4%)	1 (12.5%)	0
Elevated white blood cell count	0	0	0	0	0	1 (14.3%)	1 (2.1%)	0	0
Prolonged APTT	0	0	0	0	0	0	0	1 (12.5%)	0
Prolonged bleeding time	0	0	1 (12.5%)	0	0	0	1 (2.1%)	0	0
Urine white blood cell positive	0	0	0	0	1 (12.5%)	1 (14.3%)	2 (4.3%)	0	0
Prolonged PT	0	0	0	0	3 (37.5%)	0	3 (6.4%)	0	0
Decreased diastolic blood pressure	0	0	0	0	0	1 (14.3%)	1 (2.1%)	0	0
QT internal prolongation on ECG	0	0	0	1 (12.5%)	0	2 (28.6%)	3 (6.4%)	0	0
Decreased blood fibrinogen level	0	0	0	0	1 (12.5%)	2 (28.6%)	3 (6.4%)	0	0
Damages, toxications, and surgical complications	0	0	1 (12.5%)	0	0	0	1 (2.1%)	0	0
Subcutaneous hematoma	0	0	1 (12.5%)	0	0	0	1 (2.1%)	0	0
Disorders of the skin and subcutaneous tissues	0	0	0	0	1 (12.5%)	0	1 (2.1%)	0	0
Petechiae	0	0	0	0	1 (12.5%)	0	1 (2.1%)	0	0
Gastrointestinal diseases	1 (12.5%)	0	0	0	1 (12.5%)	0	2 (4.3%)	0	0
Gum swelling	1 (12.5%)	0	0	0	0	0	1 (2.1%)	0	0
Nausea	0	0	0	0	1 (12.5%)	0	1 (2.1%)	0	0
Disorders of the blood vessels and lymph-vessels	0	0	1 (12.5%)	3 (37.5%)	1 (12.5%)	0	5 (10.6%)	0	0
Gum bleeding	0	0	1 (12.5%)	3 (37.5%)	1 (12.5%)	0	5 (10.6%)	0	0

N, number of subjects with any AE; n, number of adverse events; *adverse event considered to be related to treatment.
APTT = activated partial thromboplastin time, DBP = diastolic blood pressure, ECG = electrocardiogram, PT = prothrombin time, WBC = white blood cell.

Table 3

Adverse events related to vicagrel.

	Vicagrel (N = 47)			
	n	Mild	Moderate	Severe
Adverse events	17 (36.1%)	16 (34.0%)	1 (2.1%)	0
Gastrointestinal diseases	2 (4.3%)	2 (4.3%)	0	0
Gum swelling	1 (2.1%)	1 (2.1%)	0	0
Nausea	1 (2.1%)	1 (2.1%)	0	0
Damages, toxicity, and surgical complications	1 (2.1%)	1 (2.1%)	0	0
Subcutaneous hematoma	1 (2.1%)	1 (2.1%)	0	0
Examination results	11 (23.4%)	10 (21.3%)	1 (2.1%)	0
Prolonged bleeding time	1 (2.1%)	1 (2.1%)	0	0
Decreased blood fibrinogen level	3 (6.4%)	3 (6.4%)	0	0
Decreased diastolic blood pressure	1 (2.1%)	1 (2.1%)	0	0
QT internal prolongation on ECG	3 (6.4%)	3 (6.4%)	0	0
Prolonged PT	3 (6.4%)	2 (4.3%)	1 (2.1%)	0
Elevated white blood cell count	1 (2.1%)	1 (2.1%)	0	0
Urine white blood cell positive	2 (4.3%)	2 (4.3%)	0	0
Subcutaneous tissues	1 (2.1%)	1 (2.1%)	0	0
Petechiae	1 (2.1%)	1 (2.1%)	0	0
Disorders of the blood vessels and lymph-vessels	5 (10.6%)	5 (10.6%)	0	0
Gum bleeding	5 (10.6%)	5 (10.6%)	0	0

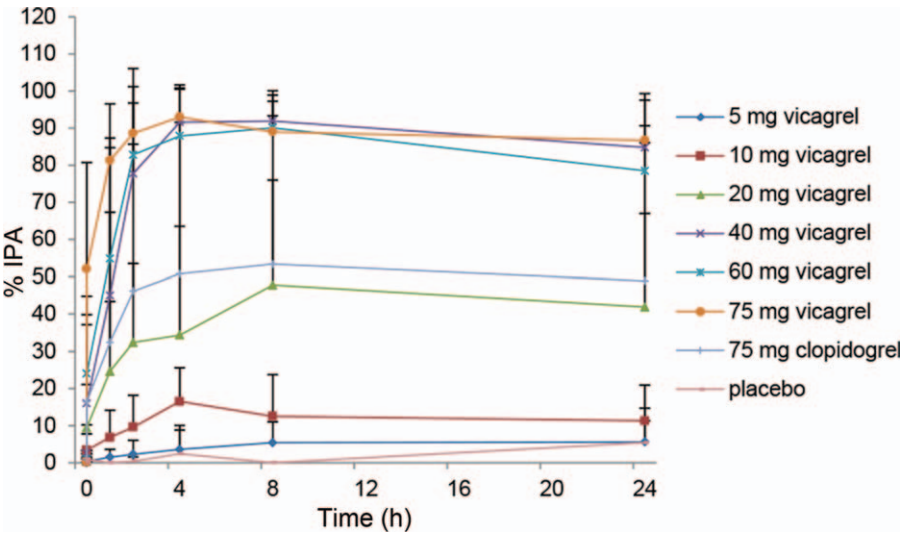

Figure 3. Mean percent inhibition platelet aggregation (%IPA) after single doses of vicagrel compared to clopidogrel and placebo at selected time points. The results represent the mean values for 8 participants (7 for the 75 mg vicagrel group) at each time point.

3.3. Vicagrel pharmacodynamics

The mean %IPA over 24 hours is shown in Figure 3. For doses ranging from 10 to 40 mg of vicagrel, the mean %IPA was increased in a dose-dependent manner. The inhibition of ADP-induced platelet aggregation occurred rapidly, peaked around 4 hours and was sustained until 24 hours post-dose (5.6 ± 5.7% for 5 mg, 11.3 ± 9.6% for 10 mg, 41.9 ± 25.2% for 20 mg, 84.8 ± 14.5% for 40 mg, 78.5 ± 12.1% for 60 mg, and 86.7 ± 10.8% for 75 mg of vicagrel). Compared with placebo, no significant differences were observed in the %IPA at 4 hours post-dose for 5 mg vicagrel or 75 mg clopidogrel ($P > .05$ for 5 mg vicagrel and 75 mg clopidogrel vs placebo). The maximum average %IPA of 91.9% for the 40 mg vicagrel dose was observed at 4 hours post-dose. Further increased doses did not significantly change the IPA values, suggesting that the %IPA peaked at 4 hours and was saturated above 40 mg.

The IPA_{max} in the 5 mg vicagrel group was not significantly different compared with the placebo, and there were no significant differences in IPA_{max} among the vicagrel doses of 40, 60, and 75 mg. Therefore, the IPA_{max} of the vicagrel doses of 10, 20, and 40 mg were selected, and the Pearson correlation test was conducted (Fig. 4). The results showed that there was a positive linear correlation between IPA_{max} and dose ($R = 0.876$, $P < .001$) for oral administration of 10 to 40 mg of vicagrel. The dose-effect between the semi-logarithm of dose and IPA_{max} was analyzed, and the results showed that the dose-effect relationship was an S-shaped curve with an EC_{50} of 20.65 mg.

For additional verification of the antiplatelet effect of vicagrel, we calculated the ΔPRU by comparing values prior to and after drug administration. The values for the mean ΔPRU vs time are shown in Figure 5. The tendency of the ΔPRU is almost consistent with that of the %IPA. The ΔPRU values increased rapidly and peaked at about 4 to 8 hours. The maximum ΔPRU value (approximately 200) was similar in the 40 mg, 60 mg, and 75 mg vicagrel groups and was maintained at 24 hours post-dose. A dose-dependent effect in the maximum ΔPRU value was observed for the 20 (ΔPRU = 134.8), 10 (ΔPRU = 48.1), and 5 mg (ΔPRU = 32.9) vicagrel doses, while the ΔPRU value for the 75 mg clopidogrel group (ΔPRU = 35.8) was relatively low, but was above the ΔPRU value for the placebo group (ΔPRU = 16.5). Therefore, the antiaggregatory effect of vicagrel was rapid and dose-dependent, with the maximal level of inhibition achieved approximately 4 hours after dosing and with 40 mg vicagrel.

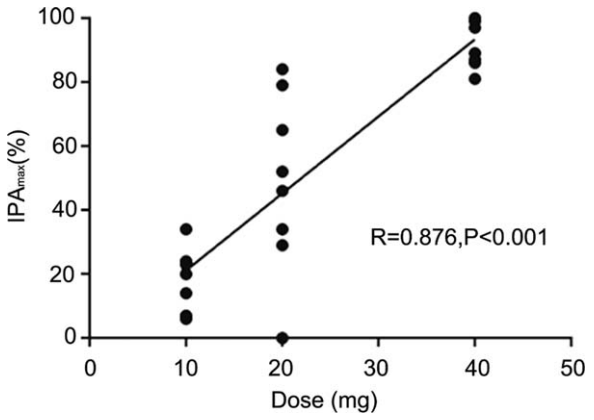

Figure 4. Mean %IPA after single vicagrel doses of 10, 20, and 40 mg. A statistically significant relationship was observed among the 3 groups. Percent inhibition platelet aggregation $(\%IPA)_{max}$ correlation coefficient (R) = 0.876, $P < .001$.

4. Discussion

Vicagrel is a new antiplatelet pro-drug based on clopidogrel sulfur lactone metabolites. This study aimed to evaluate the safety, tolerability, and PD of vicagrel in healthy Chinese subjects. The results suggest that 40 to 75 mg vicagrel inhibits ADP-induced platelet aggregation, with a fast onset of action and significantly greater potency than clopidogrel. These findings indicate that vicagrel may be a highly effective and well-tolerated antiplatelet agent.

After more than a decade after the introduction of dual antiplatelet therapy as the standard of care in the setting of acute coronary syndrome (ACS) and percutaneous coronary

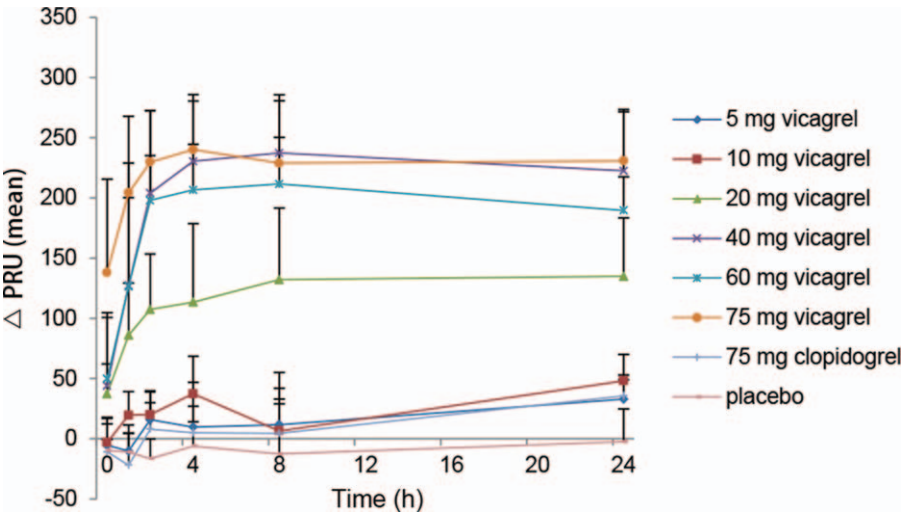

Figure 5. Mean ΔP2Y12 reaction units (ΔPRU) after single doses of vicagrel compared to clopidogrel and placebo at selected time points. The results represent the mean values for 8 participants (7 for the 75 mg vicagrel group) at each time point.

intervention (PCI),[16,17] significant issues with the use of clopidogrel were observed, mainly non-responsiveness to the two-step activation process resulting from CYP polymorphisms,[7,9,18] leading to the development of new antiplatelet agents. Based on these drawbacks, vicagrel, the acetate derivative of clopidogrel, was designed to improve its anti-platelet aggregation efficiency and therapeutic reliability in a clinical setting. Through a simple chemical modification of clopidogrel, vicagrel aimed to steer the metabolic pathway predominantly towards the active metabolites, independently of the action of CYP2C19.[19]

This study is the first to describe the PDs and safety of vicagrel, a novel thienopyridine P2Y12 inhibitor, in healthy native Chinese subjects. The results demonstrate that vicagrel was well tolerated, with a low number of drug-related AEs. Although the incidence of AEs seems to be dose-dependent, no specific AEs were dose-dependent in this study. Furthermore, none of the AEs was deemed serious or severe in intensity. Therefore, the results demonstrate that vicagrel administered orally at doses of up to 75 mg was generally safe and well-tolerated in our healthy subjects, as partially supported by a previous study that used the 5 to 15 mg range.[20] Because of the small sample size, future investigations have to be performed to identify AEs that may correlate with doses.

A previous pharmacokinetic study of the same study population showed that vicagrel is rapidly metabolized, leading to low levels of the parent drug in the blood and that the pharmacokinetics of the drug and metabolites were predictable.[12] The PD parameters showed similar results for ΔPRU and %IPA, though the %IPA value can be obtained directly from the VN-P2Y12 machine and is therefore perhaps a more reliable indicator of PDs. Compared with the placebo, there were no significant differences in the %IPA for the 5 mg vicagrel and 75 mg clopidogrel groups; however, 10 to 75 mg vicagrel induced statistically significant increases in the antiplatelet effect. These results indicate that vicagrel may have substantially higher potency than clopidogrel, and at much lower doses. Our results also showed that a single oral dose (10–40 mg) of vicagrel resulted in dose-related inhibition of the $\%IPA_{max}$, which was nearly achieved by 4 hours post-dosing. Similar to the results for the %IPA, the ΔPRU nearly peaked at 4 hours and was dose-dependent within the 10 to 40 mg range, though the patterns for the %IPA and ΔPRU differed in that effects of 5 mg vicagrel and 75 mg clopidogrel could be observed for the ΔPRU, but not for the %IPA. The timing for these effects of vicagrel is similar to that of 300 mg of clopidogrel, for which the maximal platelet effect also has been shown to be achieved at 4 hours and to be sustained until 24 hours post-dose.[21] Though inhibition of platelet aggregation in the present study peaked at 4 hours post-dosing, the antiplatelet effect was observed as early as 0.5 hours after oral administration of vicagrel, which raises the possibility that the onset time could be shorter with higher dosage. We also observed that oral doses above 40 mg did not result in higher platelet aggregation inhibition, which suggests that vicagrel prevents platelet aggregation by irreversibly inhibiting the platelet receptor P2Y12.

Although the number of AEs was slightly higher in the 40-mg group than in the 75 mg of clopidogrel, most of these AEs were mild, reversible AEs. In addition, the AUC and IPA of M15–2, the active metabolite of vicagrel, in the 5-mg group were similar to that of the 75-mg clopidogrel group. Furthermore, the results of IPA, which was the major pharmacodynamics index in this study, showed consistent dose-dependent changes within the dose range of 5 to 40 mg, while the IPA value did not increase evidently in the 60- and 75-mg groups. Therefore, we recommend that the dose of vicagrel should not be higher than 40 mg for the safety of patients.

The present study has limitations. The sample size was small, and the subjects were healthy, without the diseases for which vicagrel might be indicated. Future studies with a larger sample size would be important to verify the efficacy of vicagrel, both alone and in combination with aspirin since aspirin has been shown to attenuate the platelet response to vicagrel in mice.[22] In addition, it would be important to collect blood samples at more than 24 hours post-dose to determine the platelet aggregation recovery time.

In summary, the results provide initial evidence of the safety and efficacy of vicagrel for healthy subjects. These data should be informative for designing future phase I clinical trials for patients with atherothrombotic diseases, for which vicagrel is likely to provide improved benefit over existing therapies.

Author contributions

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