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Regular article

Pharmacokinetics and pharmacodynamics of prasugrel in healthy Japanese subjects☆

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ABSTRACT

This randomized double-blind and placebo-controlled study assessed the pharmacodynamics and pharmacokinetics of prasugrel in healthy adult Japanese male subjects after single (n = 50) and multiple (n = 40) oral administration. With a single administration of prasugrel (2–30 mg), the plasma concentration of the active metabolite increased rapidly, reached a maximum at 30 min after administration, and then decreased rapidly within 4 h. The 5 mg and higher doses prevented ADP-induced platelet aggregation in a dose-dependent manner. Further analyses showed that 30 mg prasugrel exhibited the peak inhibition, and 20 mg prasugrel showed a nearly equivalent effect. With multiple doses (2.5–10 mg), the pharmacokinetic parameters on Day 1 and Day 7 were similar, and no accumulation attributable to multiple dosing was observed. The inhibitory effect on ADP-induced platelet aggregation increased with doses from 2.5 to 7.5 mg, and reached the peak level at 7.5 mg. Regarding safety, all of the drug-related adverse events observed were mild, and there were no clinically significant bleeding-related adverse events. This study indicates that a single oral administration of prasugrel at a dose of up to 30 mg and a maintenance dose of up to 10 mg are tolerated in Japanese healthy subjects.

1. Introduction

Prasugrel is a new-generation thienopyridine anti-platelet drug. After oral administration, prasugrel is fully and rapidly hydrolyzed by intestinal carboxylesterase to intermediate metabolites, most of which are further metabolized in the small intestine and liver by CYP P450 into an active metabolite [1]. The active metabolite binds irreversibly to the platelet $P2Y_{12}$ receptor [2–4]. Prasugrel is reported to exhibit more potent inhibition of platelet aggregation, rapid onset of action, and minimal interindividual variability in efficacy [5–8] as compared with clopidogrel.

Prasugrel is already used for the reduction of atherothrombotic cardiovascular events in patients undergoing percutaneous coronary intervention in the USA, EU, and other countries. The regimen consisting of a 60-mg loading dose and 10-mg maintenance doses plus aspirin has shown a significant reduction in cardiovascular events (death, myocardial infarction, and stroke) compared with clopidogrel in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38) [9]. It was also reported that prasugrel is associated with an increased risk of TIMI major bleeding. Based on analyses of prespecified clinical features in TRITON-TIMI 38, body weight <60 kg was identified as one of the risk factors for bleeding.

Prasugrel active metabolite exposure is increased with decreased body weight [10–13]. A study in healthy Asian subjects showed that exposure to the prasugrel active metabolite was greater and the inhibitory effect on platelet aggregation was more potent in Asian subjects than in Caucasians [14]. It has also been confirmed that prasugrel shows a more rapid active metabolite generation and antiplatelet effect in Chinese subjects than in Caucasians [15]. Because the average body weight of Japanese is less than Caucasians, it is expected that Japanese subjects receive a lower dose than that prescribed in the USA and EU.

The aim of this study was to assess the safety, pharmacodynamics, and pharmacokinetics of prasugrel in healthy adult Japanese male subjects after a single and multiple oral administration.

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2. Materials and methods

2.1. Subjects and study design

Both the single administration study and multiple dose study had a randomized, double-blind, and placebo-controlled design. In the single administration study, 50 healthy Japanese male subjects aged 20–40 years [(8 subjects for each dose of prasugrel and 2 for each placebo) x 5 doses (2, 5, 10, 20, and 30 mg)] were enrolled. Each dose of study drug or placebo was administered in the morning after overnight fasting.

In the multiple administration study, 40 healthy Japanese male subjects aged 20–45 years [(8 subjects for each dose of prasugrel and 2 for each placebo) x 4 doses (2.5, 5, 7.5, 10 mg)] were enrolled. The study drug was orally administered once daily for 7 days (after at least 10 h of fasting on Days 1 and 7, after breakfast on Days 2 through 6).

The present study was conducted in accordance with the Declaration of Helsinki in compliance with Good Clinical Practice (GCP) and with the approval of the institutional review board. Written informed consent to participate in the study was obtained from subjects before their participation in the study.

2.2. Pharmacokinetics

In the single administration study, blood samples were collected before administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h post-dose for analysis of the plasma concentration of active metabolite of prasugrel. In the multiple dose study, samples were collected before administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h post-dose on Days 1 and 7. The plasma concentration of active metabolite of prasugrel was measured using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Based on the plasma concentration of the active metabolite, pharmacokinetic parameters were assessed. An Inertsil ODS-3 column (G. L Sciences Inc.) was used as the HPLC column. The LC mobile phase was methanol with 1% formic acid (54:46), and the methanol and 1% formic acid were mixed using an HPLC pump. The rate of flow was 0.25 mL/min and the injection volume 10 μL. A quadrupole tandem mass spectrometer was used for MS (model API4000; Applied Biosystems, Inc.). From the chromatogram obtained, the peak area ratio (Y) for the active metabolite MP and I. Std. was calculated using the LC-MS/MS data-processing software Analyst. Then, using the calibration curve obtained by linear regression with the preparation concentration as X and an applied weighting of $1/X^2$, quantitative calculations were made by the internal standard method.

Parameters calculated were area under the plasma concentration–time curve up to the last quantifiable time ($AUC_{0\text{-}tz}$), area under the plasma concentration–time curve up to infinity ($AUC_{0\text{-}inf}$), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), and terminal elimination half-life ($t_{1/2}$) in both studies. In the single administration study, WinNonlin-Pro version 4.1 (Pharsight Corporation, Mountain View, CA) was used for calculation of pharmacokinetic parameters, and S-plus 6.2J for Windows (Mathematical Systems, Inc., Tokyo, Japan) was used for the data handling. In the multiple administration study, area under the plasma concentration–time curve during dosing interval (AUC_{tau}) and cumulative coefficient (R_{obs}) were also examined. R_{obs} was calculated as the ratio of AUC_{tau} values on Days 1 and 7. WinNonlin-Pro version 5.0.1 (Pharsight Corporation) was used for calculation of pharmacokinetic parameters other than R_{obs}. S-plus 6.2J for Windows (Mathematical Systems, Inc., Tokyo, Japan) was used for the data handling and calculation of R_{obs}.

2.3. Pharmacodynamics

In the single administration study, blood samples were collected before administration and at 1, 2, 4, 8, 24, 48, 96, and 168 h after administration. In the multiple administration study, blood sampling was before administration and at 4 h after dosing on Days 1, 3 and 5, at 1, 4, and 8 h after dosing on Day 7, and at 24, 48, and 96 h after the final administration. The pharmacodynamics measurements were determined by the light transmission method in response to 5 and 20 μM of adenosine diphosphate (ADP). CHRONO-PAR ADP REAGENT (Chrono-Log Corp., Cat No. 384) was used as ADP. At each measuring point, the maximum platelet aggregation (MPA) was measured using a platelet aggregation analyzer (MC Medical Inc., MCM Hematracer 313M) using light transmission. Based on the MPA measured at each blood-sampling time point after the start of administration, the IPA with respect to ADP (5, 20 M) was calculated using the following formula.

$$\mathrm{IPA}(\%) = \left(\frac{\text{MPA at screening} - \text{MPA at each measuring point}}{\text{MPA at screening}}\right) \times 100$$

In the multiple administration study, the platelet reactivity index (PRI), as determined by vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay, was also assessed. The PRI was calculated for each blood-sampling time point following the start of administration using the following formula.

$$\mathrm{PRI} = \left(\frac{\mathrm{MFI_{PGE1}} - \mathrm{MFI_{ADP}}}{\mathrm{MFI_{PGE1}}}\right) \times 100$$

$$\mathrm{MFI_{PGE1}} = \mathrm{MFI(T1)} - \mathrm{MFI(T3)}$$

$$\mathrm{MFI_{ADP}} = \mathrm{MFI(T2)} - \mathrm{MFI(T3)}$$

MFI is mean fluorescence intensity; PGE1, prostaglandin E1; MFI(T1), the value of MFI after stimulating the sample with PGE1, when stained with anti-phosphorylated VASP antibodies; MFI(T2), the value of MFI after stimulating the sample with ADP and PGE1, when stained with anti-phosphorylated VASP antibodies; and MFI(T3), the value of MFI after stimulating the sample with ADP and PGE1, when stained with negative control antibodies.

2.4. Evaluation of bleeding times

The bleeding time was measured by the Ivy method. In the single dose study, bleeding time was measured before administration and at 4, 24, and 168 h after dosing. In the multiple administration study, it was measured before administration, at 4 h after dosing on Days 1 and 7, at 24 h after dosing on Day 7, and at 168 h after the final administration.

2.5. Safety

The safety and tolerability of prasugrel were evaluated by assessing the incidence of adverse events. In the single administration study, the incidence of adverse events from the time of administration to 168 h after dosing was evaluated. In the multiple dose study, evaluation period of adverse events was from Day 1–96 h after the final dosing.