Pharmacokinetics and Pharmacodynamics of Ticagrelor and Prasugrel in Healthy Male Korean Volunteers

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ABSTRACT

Purpose: A combination of clopidogrel and aspirin is the standard treatment for patients with acute coronary syndrome and those undergoing percutaneous coronary intervention. Two novel antiplatelet agents, ticagrelor and prasugrel, have been shown to rapidly and more effectively inhibit the $P2Y_{12}$ receptor compared with clopidogrel. The aim of this study was to evaluate and compare the pharmacokinetics (PK) and pharmacodynamics (PD) of ticagrelor and prasugrel in healthy male Korean volunteers.

Methods: Two separate studies were conducted. One study was performed by using a single-sequence, open-label, crossover design in 12 volunteers who received a single oral dose of ticagrelor (180 mg) and then a single oral dose of prasugrel (60 mg for 4 volunteers and 30 mg for 8 volunteers) with a 7-day washout period. The other study was a randomized, open-label, parallel-group investigation in which 8 volunteers received a single oral dose of prasugrel (10 mg for 4 volunteers and 30 mg for 4 volunteers). In each study, blood samples for PK and platelet aggregation inhibition analysis were serially collected after the administration of each dose. Plasma concentrations of ticagrelor, AR-C124910XX (the active metabolite of ticagrelor), R-95913 (the inactive metabolite of prasugrel), and R-138727 (the active metabolite of prasugrel) were measured by using a validated LC-MS/MS method. PK was analyzed by using a noncompartmental method. Maximal platelet aggregations were assessed with light transmission aggregometry after induction with 20 μmol/L of adenosine diphosphate.

Findings: Twenty healthy male Korean volunteers participated in the 2 studies. Plasma concentrations of ticagrelor and AR-C124910XX were obtained from 12 subjects, R-95913 from 20 subjects, and R-138727 from 8 subjects. Both ticagrelor and prasugrel were rapidly absorbed, with the shortest median T_{max} of 2.0 and 2.25 hours for ticagrelor and AR-C124910XX, respectively, and a T_{max} of 0.5 hour for both R-95913 and R-138727. Strong inhibition of platelet aggregation was shown after administration of both ticagrelor and prasugrel, with slightly stronger and more rapid inhibition with prasugrel in the tested doses. Inhibitory activities of prasugrel lasted longer than those of ticagrelor, reflecting the difference in binding kinetics between the 2 drugs.

Implications: Prasugrel 30 and 60 mg exhibited slightly stronger, more rapid, and sustainable platelet inhibitory effects compared with ticagrelor 180 mg. These differing effects should be considered when determining the efficacy and adverse effects of ticagrelor and prasugrel. ClinicalTrials.gov identifier:

Accepted for publication January 19, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.01.010
0149-2918/$ - see front matter

NCT01876797 and NCT02075268. (*Clin Ther.* 2015;37:563–573)

Key words: antiplatelet agents, healthy volunteers, pharmacodynamics, pharmacokinetics, prasugrel, ticagrelor.

INTRODUCTION

Thromboembolic disorders, either venous or arterial, are a major health problem worldwide and are associated with mortality and disabilities.[1] Because platelets predominate in arterial thrombi compared with venous thrombi, antiplatelet drugs are the mainstay for the prevention and treatment of such disorders.[2,3] Antiplatelet therapy is widely used for the treatment of atherosclerotic coronary artery disease. Guidelines formulated by both the American College of Cardiology/American Heart Association and the European Society of Cardiology recommend the use of dual antiplatelet therapy with aspirin in combination with a $P2Y_{12}$ receptor inhibitor in patients with acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI).[2,4] These recommendations are primarily based on randomized, Phase III clinical trials of $P2Y_{12}$ inhibitors such as clopidogrel, prasugrel, and ticagrelor. However, few East Asian patients participated in such trials, especially for the newer agents (eg, ticagrelor, prasugrel), and there is increasing evidence indicating different treatment effects and adverse event profiles between East Asian and white subjects.[1]

Ticagrelor is an orally administered, non-thienopyridine, cyclopentyltriazolo-pyrimidine that was approved in the European Union in 2010 and in the United States in 2011.[5,6] The drug binds reversibly and blocks adenosine diphosphate (ADP) receptors of subtype $P2Y_{12}$.[7] Ticagrelor is an allosteric inhibitor, which binds to a different site than the ADP-binding site. Although ticagrelor possesses pharmacologic activity, it also has a known active metabolite, AR-C124910XX, derived from cytochrome P-450 (CYP) 3A4/5 metabolism whose concentration in blood is approximately one third of that of the parent compound.[8] It does not require metabolic activation for its therapeutic effect, which may explain its low interpatient variations in drug exposure compared with clopidogrel.[9] A previous study found that ticagrelor exerts stronger, faster, and more consistent platelet inhibition compared with clopidogrel in both healthy subjects and in patients with stable coronary artery disease.[7]

Prasugrel is a third-generation thienopyridine agent that was approved in the European Union, the United States, and in other regions in 2009 for the treatment of ACS in patients undergoing PCI.[2] Similar to clopidogrel, prasugrel is a prodrug that is biotransformed into an inactive metabolite (R-95913) and pharmacologically active metabolite (R-138727). R-95913 is formed via hydrolysis, predominantly by intestinal human carboxylesterase 2, whereas CYP2B6, CYP2C9, CYP2C19, and CYP3A4 catalyze the formation process of the R-138727 in the second reaction. R-138727 binds irreversibly to ADP receptors of $P2Y_{12}$ by forming disulfide bridges between extracellular cysteine residues at positions Cys17 and Cys270 to prevent platelet activation.[10] The metabolism of prasugrel into R-138727 is believed to be less affected by genetic variations in CYP2C19 and CYP2C9 compared with clopidogrel and is less affected by drug interactions in CYP3A4 metabolism, leading to less interpatient variations in the level of the active metabolite.[11]

The aim of the present study was to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of the newer antiplatelet agents, ticagrelor and prasugrel, in healthy male Korean subjects.

SUBJECTS AND METHODS

Subjects

Healthy male Korean volunteers between the ages of 19 and 45 years were enrolled in this study. All subjects were in good health, as determined by the results of their medical history, physical examinations, vital signs, routine clinical laboratory tests, and ECGs. Study subjects had a body mass index between 18 and 30 kg/m^2 and were negative for HIV, syphilis, and hepatitis B and C virus. They had no history of alcoholism, heavy smoking, or hypersensitivity to ≥ 1 drug. Volunteers who had donated blood within the past 2 months, who had been recipients of a transfusion within the past 1 month, or who had taken any prescription medication within 2 weeks of the start of the study were excluded.

All subjects provided written informed consent before participation, and the analyses were conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice