Effect of Food on the Pharmacokinetic Properties of the Oral Sarpogrelate Hydrochloride Controlled-Release Tablet in Healthy Male Korean Subjects

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ABSTRACT

Background: A new controlled-release formulation of sarpogrelate, a 5-hydroxytryptamine receptor subtype 2 antagonist that blocks serotonin-induced platelet aggregation, has been developed for once-daily administration.

Objective: This study evaluated the effect of food on the pharmacokinetic properties of controlled-release sarpogrelate (sarpogrelate CR) in healthy volunteers.

Methods: A randomized, open-label, two-period, two-treatment crossover study was performed in healthy male Korean subjects. Following an overnight fast, a single dose of sarpogrelate CR 300 mg was administered either in the fasted condition or immediately after a high-fat breakfast. Pharmacokinetic parameters were calculated using a noncompartmental analysis. Tolerability was determined using clinical laboratory testing and physical examination, including vital sign measurements, electrocardiography, and interviews with the volunteers regarding adverse events (AEs).

Results: A total of 24 healthy subjects were enrolled, 23 of whom completed the study (mean [range] age, 26 years [21–45]; weight, 68.1 kg [56.0–79.9]; body mass index, 22.1 kg/m^2 [18.8–25.0]). Sarpogrelate C_{max} and AUC_{last} were decreased In the fed condition compared with those in the fasted condition, with geometric mean ratios (90% CI) of 0.4868 (0.4041–0.5864) and 0.7394 (0.6809–0.8028), respectively. T_{max} was delayed from 0.75 to 4.0 hours after a high-fat meal, but the fed condition exhibited a similar elimination profile to that of the fasted condition. The most commonly reported AE was headache (n = 2), and other AEs were reported in 1 subject each. All of the AEs were considered mild in intensity, and the participants recovered without treatment.

Conclusions: Compared with the administration of sarpogrelate CR 300 mg in the fasted condition, administration with food was associated with a decreased rate and extent of absorption, as assessed by C_{max} and AUC_{last}, respectively. The drug was well-tolerated by the healthy subjects in this study. (*Clin Ther*. 2013;35:1038–1044)

Key words: 5-HT receptor antagonist, food effect, healthy subjects, pharmacokinetics.

INTRODUCTION

5-Hydroxytryptamine (5-HT, serotonin) is important for a variety of physiologic functions, including platelet aggregation, smooth muscle contraction, appetite, cognition, perception, mood, and other central nervous system functions, by acting on a large number of 5-HT receptor subtypes.[1,2] Among them, 5-HT_{2A} receptor is associated with the contraction of vascular smooth muscle, platelet aggregation, thrombus formation, and coronary artery spasms.[3] Sarpogrelate hydrochloride

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((±)-1-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-3-(dimethyl amino)-2-propyl hydrogen), a selective 5-HT_{2A} receptor antagonist, was introduced as a therapeutic agent for ischemic diseases associated with thrombosis.[3–5] Sarpogrelate and its active metabolite, M-1 ((±)-1-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-3-(dimethyl amino)-2-propanol), inhibits responses to 5-HT mediated by 5-HT_{2A} receptors, such as platelet aggregation, vasoconstriction, and vascular smooth muscle proliferation.[6–8] Since it was approved for the treatment of peripheral arterial disease in 1993,[9] sarpogrelate hydrochloride has been used for the treatment of patients with coronary artery disease, angina pectoris, atherosclerosis, and type 2 diabetes mellitus.[4,10–13]

Sarpogrelate hydrochloride is rapidly absorbed in the gastrointestinal tract when administered orally, and $t_{1/2}$ of sarpogrelate ranges from 0.6 to 0.8 hours in healthy subjects.[14] Because of its short half-life, the immediate-release (IR) formulation of sarpogrelate hydrochloride is administered three times a day. To reduce the frequency and inconvenience of multiple administrations, a once-daily formulation of sarpogrelate hydrochloride is being developed. This controlled-release (CR) formulation of sarpogrelate hydrochloride was designed as a double-layered tablet to ensure immediate treatment effects and to reduce the number of required administrations, with a T_{max} of 0.9 hours and a half-life of 4.4 hours.[15]

Interactions between orally administered drugs and food intake have been shown to affect drug bioavailability.[16,17] With certain drugs, food interactions can be clinically significant, resulting in altered efficacy and/or toxicity.[17] Because sarpogrelate CR might be taken with food, modification of the dosing regimen may be required in the event of any subsequent significant change in the pharmacokinetic properties. Therefore, the objective of the present study was to evaluate the effect of food intake on sarpogrelate pharmacokinetic properties following single-dose administration. According to regulatory guidance for formally assessing the effects of food on orally administered drugs to guide clinical administration, sarpogrelate CR was administered with a high-fat, high-calorie meal to maximize the potential effect of food on bioavailability.[18,19]

SUBJECTS AND METHODS

Inclusion and Exclusion Criteria

Eligible subjects were healthy male Korean volunteers between the ages of 20 and 55 years and with a body mass index (BMI) of 18.5 to 25 kg/m^2. The following exclusion criteria were used in this study: a history of cardiovascular, hepatic, renal, endocrinal, gastrointestinal, neurologic, or hemorrhagic disease; a bleeding risk, such as a recent operation or uncontrolled hypertension; clinically significant findings on clinical laboratory testing (hematology, blood chemistry, and urinalysis, including hepatitis B, C, and HIV tests), physical examination, or electrocardiography; positive urine test result for drugs of abuse (eg, amphetamines, barbiturates, cocaine, opioids, benzodiazepines); a history of hypersensitivity to sarpogrelate or any other antiplatelet agents; and any medication history within 1 week prior to the first administration of the study drug. All of the subjects provided a written informed consent before enrollment.

Study Design

This randomized, open-label, two-period, two-treatment crossover study was conducted between July and August 2011. A single 300-mg oral dose of sarpogrelate CR (DP-R202) was administered in the fed and fasted conditions in each study period. To ensure that no carryover effect was observed, each period was separated by a 7-day washout, corresponding to >7-fold the expected half-life of sarpogrelate. All subjects were assigned, using a predetermined randomization code produced with SAS software (SAS Institute, Inc, Cary, North Carolina) by the Samsung Biomedical Research Institute. The institutional review board at Samsung Medical Center, Seoul, Korea, approved the protocol, and the study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice.[20]

Subjects were admitted to the Clinical Trial Center at Samsung Medical Center on the day before the administration of the study drug. Food was controlled and standardized in each treatment period and in all subjects. Following an overnight fast of at least 10 hours, subjects were administered a single 300-mg dose of sarpogrelate CR orally with 240 mL of water in the fed or fasted condition. For the fed condition, a high-fat, high-calorie breakfast (900 kcal, fat ≥35%) was provided 30 minutes prior to drug administration. The subjects were to have consumed the total contents of the meal within 20 minutes. Water intake was not allowed from 1 hour before to 1 hour after drug administration. A standardized lunch