Pharmacokinetic Comparison of Sustained- and Immediate-Release Oral Formulations of Cilostazol in Healthy Korean Subjects: A Randomized, Open-Label, 3-Part, Sequential, 2-Period, Crossover, Single-Dose, Food-Effect, and Multiple-Dose Study

Donghwan Lee, MD[1]; Lay Ahyoung Lim, MD[1]; Seong Bok Jang, PhD[1]; Yoon Jung Lee, PhD[1]; Jae Yong Chung, MD, PhD[1]; Jong Rak Choi, MD, PhD[2]; Kiyoon Kim, MS[3]; Jin Woo Park, PhD[3]; Hosang Yoon, MS[3]; Jaeyong Lee, MS[3]; Min Soo Park, MD, PhD[4]; and Kyungsoo Park, PhD, MD[1]

[1]Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Pacificpharma Corporation, Seoul, Korea; and [4]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Background: A sustained-release (SR) formulation of cilostazol was recently developed in Korea and was expected to yield a lower C_{max} and a similar AUC to the immediate-release (IR) formulation.

Objective: The goal of the present study was to compare the pharmacokinetic profiles of a newly developed SR formulation and an IR formulation of cilostazol after single- and multiple-dose administration and to evaluate the influence of food in healthy Korean subjects. This study was developed as part of a product development project at the request of the Korean regulatory agency.

Methods: This was a randomized, 3-part, sequential, open-label, 2-period crossover study. Each part consisted of different subjects between the ages of 19 and 55 years. In part 1, each subject received a single dose of SR (200 mg × 1 tablet, once daily) and IR (100 mg × 2 tablets, BID) formulations of cilostazol orally 7 days apart in a fasted state. In part 2, each subject received a single dose of the SR (200 mg × 1 tablet, once daily) formulation of cilostazol 7 days apart in a fasted and a fed state. In part 3, each subject received multiple doses of the 2 formulations for 8 consecutive days 21 days apart. Blood samples were taken for 72 hours after the dose. Cilostazol pharmacokinetics were determined for both the parent drug and its metabolites (OPC-13015 and OPC-13213). Adverse events were evaluated through interviews and physical examinations.

Results: Among the 92 enrolled subjects (66 men, 26 women; part 1, n = 26; part 2, n = 26; part 3, n = 40), 87 completed the study. In part 1, all the primary pharmacokinetic parameters satisfied the criterion for assumed bioequivalence both in cilostazol and its metabolites, yielding 90% CI ratios of 0.9624 to 1.2323, 0.8873 to 1.1208, and 0.8919 to 1.1283 for C_{max} and 0.8370 to 1.0134, 0.8204 to 0.9807, and 0.8134 to 0.9699 for AUC_{0-last} of cilostazol, OPC-13015, and OPC-13213, respectively. In part 2, food intake increased C_{max} and AUC significantly ($P < 0.0001$), yielding geometric mean ratios of 3.2879, 2.9894, and 3.0592 for C_{max} and 1.7001, 1.7689, and 1.6976 for AUC_{0-last} of cilostazol, OPC-13015, and OPC-13213. In part 3, only the C_{ssmax} of clilostazol in the reference formulation did not satisfy the criterion for assumed bioequivalence, yielding 90% CI ratios of 1.2693 to 1.4238 and 1.2038 to 1.3441, respectively. When each dose was normalized, the C_{max} for the SR formulation was significantly lower ($P < 0.005$ for cilostazol). Headache was the most frequently noted adverse effect (part 1, a total of 14 subjects with the IR formulation and 14 with the SR formulation; part 2, a total of 10 without food and 23 with a high-fat meal; part 3, a total of 10 with the IR formulation and 24 with the SR formulation), followed by nausea (part 1, none; part

Part of this work was presented at the annual meeting of the American Association of Pharmaceutical Scientists; November 8-12, 2009; Los Angeles, California.

Accepted for publication October 25, 2011.
doi:10.1016/j.clinthera.2011.10.024
0149-2918/$ - see front matter

2, only 1 without food and 3 with a high-fat meal; part 3, a total of 3 with the IR formulation and 3 with the SR formulation), and then dizziness (parts 1 and 2, none; part 3, a total of 4 with the IR formulation and 5 with the SR formulation). All other AEs, including fever, cough, vomiting, palpitation, diarrhea, and epigastric pain, occurred in <3 subjects.

Conclusions: These findings suggest that in this select group of healthy Korean volunteers, the SR formulation of cilostazol was not significantly different in AUC compared with that of the IR formulation, although it did display a significantly lower C_{max} per dose in both the single- and multiple-dose groups. Food significantly increased the bioavailability of the SR formulation. The cilostazol SR and IR formulations were well tolerated in all parts of the study, with no serious adverse events reported. ClinicalTrials.gov identifier: NCT01455558. (*Clin Ther.* 2011;33:2038–2053)

Key words: cilostazol, circadian variation, food effect, multiple doses, pharmacokinetics, sustained-release.

INTRODUCTION

Cilostazol inhibits phosphodiesterase type 3 activity and adenosine uptake, which induces inhibition of platelet aggregation, vasodilation, and antithrombosis, improvement of the lipid profile, and attenuation of proliferation of vascular smooth muscle cells.[1,2] Thus, cilostazol is used not only to treat intermittent claudication[3,4] but also to prevent restenosis of the coronary artery[5,6] and act as secondary prevention of stroke.[7]

Since the launch of cilostazol* in 1988, it has been approved and used in many countries as an immediate-release (IR) tablet formulation with BID administration. However, taking a medication regularly twice a day is inconvenient for patients. Also, the IR formulation is rapidly absorbed in the upper gastrointestinal tract and can reach C_{max} within a short time, which could be related to acute adverse events.[5,8,9] To overcome these drawbacks of the IR formulation, the sustained-release (SR) formulation, with once-daily administration, was developed. This SR formulation was expected to have a lower C_{max} and an amount of exposure similar to that of the IR formulation and to help improve patient compliance by reducing the frequency of dosing and adverse events.

*Trademark: Pletal® (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan).

This 3-part, randomized, open-label, 2-period, crossover, clinical study was conducted to investigate single-dose pharmacokinetics (part 1), the effects of food on pharmacokinetics (part 2), multiple-dose pharmacokinetics (part 3), and the tolerability of the new SR formulation of cilostazol in healthy Korean subjects. The aim of the present study was to compare the pharmacokinetic properties of the cilostazol SR formulation with those of the IR formulation. This study was conducted as part of a product development project at the request of the Korean regulatory agency.

SUBJECTS AND METHODS

Subjects

Eligible subjects were healthy male or female volunteers between the ages of 19 and 55 years and within 20% of their ideal body weight, and with no congenital abnormality or chronic disease.

Exclusion criteria included history of cardiovascular, pulmonary, renal, endogenous, gastrointestinal, hematologic, neurologic, or hemorrhagic disease; clinically significant findings on routine laboratory (hematology, serum chemistry, and urinalysis) or ECG tests; use of prescription drugs within 14 days before the study that had the potential to interact with the study medication; and use of any substance that could induce cytochrome P450 3A4 synthesis (eg, St. John's wort, other herbal medications).

Female subjects were required to have negative results on a serum pregnancy test before the study, and those who were of childbearing potential agreed to use one of the following medically accepted methods of contraception during the entire study period: abstinence, documented tubal ligation for at least 1 year before enrolling in the study, documented placement of an intrauterine device with a proven failure rate of <1% per year, or double barrier methods (a spermicide plus a male condom or female diaphragm).

This study was approved by the institutional review board of Yonsei University Severance Hospital (Seoul, Korea) and performed in accordance with the Declaration of Helsinki[10] and Korean Good Clinical Practice.[11] All subjects gave written informed consent before study enrollment.

Study Design

This randomized, open-label, 2-period, crossover study consisted of 3 parts: a single-dose study (part 1), a food-effect study (part 2), and a multiple-dose study (part