TCP Transl Clin Pharmacol
2016;24(4):183-188
http://dx.doi.org/10.12793/tcp.2016.24.4.183

ORIGINAL ARTICLE

Pharmacokinetic characteristics of cilostazol 200 mg controlled-release tablet compared with two cilostazol 100 mg immediate-release tablets (Pletal) after single oral dose in healthy Korean male volunteers

Jin Dong Son[1,4], Sang Min Cho[2], Youn Woong Choi[2], Soo-Hwan Kim[3], In Sun Kwon[4], Eun-Heui Jin[4], Jae Woo Kim[4] and Jang Hee Hong[1,4,5]*

[1]Department of Medical Science, College of Medicine, Chungnam National University, Daejeon 35015, republic of Korea, [2]Korea United Pharm.Inc., Seoul 06116, Republic of Korea, [3]Caleb Multilab Inc., Seoul 06745, Republic of Korea, [4]Clinical Trials Center, Chungnam National University Hospital, Daejeon 35015, South Korea, [5]Department of Pharmacology, College of Medicine, Chungnam National University, Daejeon 35015, Republic of Korea

*Correspondence: J.H. Hong; Tel: +82-42-280-6940, Fax: +82-42-280-6940, E-mail: boniii@cnu.ac.kr

Received 8 Sep 2016
Revised 28 Nov 2016
Accepted 29 Nov 2016

Keywords
Cilostazol,
OPC-13015,
OPC-13213,
bioequivalence,
pharmacokinetics

pISSN: 2289-0882
eISSN: 2383-5427

Cilostazol controlled-release (CR) tablets have recently been developed by Korea United Pharm (Seoul, Korea). The tablets use a patented double CR system, which improves drug compliance by allowing "once daily" administration and reduces adverse events by sustaining a more even plasma concentration for 24 h. We conducted an open, randomized, two-period, two-treatment, crossover study to compare the pharmacokinetic (PK) characteristics and tolerability of cilostazol when administered to healthy Korean male volunteers as CR or immediate release (IR) tablets (Pletal, Korea Otsuka Pharmaceutical Co., Gyeonggi-do, Korea). Each volunteer was randomly allocated to receive a single tablet of cilostazol CR (200 mg) or two tablets of cilostazol IR (100 mg) with a 7-day washout period between treatments. Plasma cilostazol, OPC-13015 (3,4-dehydrocilostazol), and OPC-13213 (4′-*trans*-hydroxycilostazol) were assayed using liquid chromatography-tandem mass spectrometry for PK analysis. Thirty participants completed the study with no clinically relevant safety issues. The peak concentrations (C_{max}, mean ± SD) of cilostazol CR and cilostazol IR were 1414.6 ± 49.3 and 1413.1 ± 35.2 ng/mL, respectively, and the areas under the plasma concentration–time curve from 0 to the last concentration (AUC_{last}) were 23928.7 ± 65.9 and 25312.0 ± 62.6 ng·h/mL, respectively. The geometric mean ratios (cilostazol CR/ cilostazol IR, GMR) of the C_{max} and AUC_{last} values were 1.001 (90% CI: 0.822, 1.220) and 0.945 (90% CI: 0.814, 1.098), respectively. The frequencies of adverse events were similar. The present study showed that cilostazol PK and tolerability were comparable when administered to healthy Korean men, regardless of whether administered as cilostazol CR or IR.

Introduction

Cilostazol is an antithrombotic and vasodilating agent that was synthesized by Otsuka Pharmaceutical Co. (Chiyoda, Tokyo, Japan) in 1978. Cilostazol has been widely used for the treatment of ischemic symptoms, including the ulceration, pain, and coldness of the extremities resulting from chronic arterial occlusion. [1–3] Cilostazol inhibits platelet aggregation through inhibition of cyclic AMP phosphodiesterase in platelets. Cilostazol also inhibits phosphodiesterase in vascular smooth muscle cells and

thereby exerts its vasodilatory effect without significant changes in blood pressure and pulse rate.[4] In a 12-week, double-blind clinical trial in patients with intermittent claudication, initial claudication distance and absolute claudication distance were significantly improved by 35% and 41%, respectively, in the participants who received cilostazol 100 mg twice daily (n = 52) compared with participants who received placebo (n = 25) ($P < 0.01$).[5] In a 24-week, double-blind clinical trial in patients with peripheral arterial disease, absolute claudication distance was significantly improved by 54% in the participants who received cilostazol 100 mg twice daily (n = 227) compared with participants who received pentoxifylline (n = 232) ($P < 0.001$).[6]

The cilostazol controlled-release (CR) formula is composed of a matrix-type polymer and carbomer in which sol–gel transition occurs in accordance with pH. Cilostazol CR uses a carbomer that maintains CR of conventional matrix structures and has sol–gel transition properties, thus preventing a sudden release of a drug caused by a collapse of the matrix structure during a late stage of elution. Because the CR formulation continuously releases the drug compared with the conventional immediate release (IR) drug, it is possible to maintain an effective blood concentration of the drug for a long time. The level of the plasma concentration and side effects resulting from the administration of the conventional IR drug can be reduced, and the compliance of the patients can be improved by reducing the frequency of administration. A previous study suggested that the cilostazol CR formulation may provide prolonged drug absorption and sufficient therapeutic efficacy, potentially serving as an oral once-daily cilostazol formulation to improve patient compliance.[7]

In the present study, we aimed to evaluate and compare the PK characteristics and tolerability of cilostazol CR and IR after a single tablet of cilostazol 200 mg CR or two tablets of cilostazol 100 mg IR in healthy Korean male volunteers.

Methods

Participants

Healthy Korean male volunteers between 19 and 55 years old were enrolled into this study. Medical histories, vital signs (blood pressure, pulse rate, and body temperature), physical examinations, laboratory tests (hematology, clinical chemistry, coagulation, urinalysis, electrolyte, serology tests, and urine drug screening), and electrocardiography (ECG) results were assessed in all the potential participants. Exclusion criteria included clinically significant medical history, abnormality of vital signs (systolic blood pressure (SBP)) ≤100 mmHg or ≥145 mmHg, diastolic blood pressure (DBP) ≤50 mmHg or ≥95 mmHg or pulse rate (PR) ≥100 /min), drug hypersensitivity, out of reference range of the prothrombin time (PT) or the activated partial thromboplastin time (aPTT) (reference ranges of PT and aPTT tests were 11–15 s and 22.4–40.4 s, respectively).

Study design

The present study was conducted as a randomized, open-label, single-dose, 2-treatment, 2-period, 2-way crossover design. Participants were randomly assigned to 'Sequence I (A–B sequence)' or 'Sequence II (B–A sequence)' ('Sequence I':'Sequence II' = 1:1) using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA). Participants assigned to 'Sequence I' received one tablet of reference drug (cilostazol 100 mg IR (Pletal); Korea Otsuka Pharmaceutical Co., Gyeonggi-do, Korea) twice daily every 12 h for a day (two tablets) in period 1, and then one tablet of test drug (cilostazol 200 mg CR; Korea United Pharm., Seoul, Korea) once daily for a day (one tablet) in period 2. Each period was separated by a 7-day washout. Eligible participants were admitted to the Clinical Trials Center, Chungnam National University Hospital, on a day before investigational product administration (Day –1 or Day 8). On Day 1 or Day 9, the participants received one tablet of reference drug (100 mg) twice daily every 12 h or one tablet of test drug (200 mg) once daily with 240 mL of water after an overnight fast from 10 pm on the day before administration. During the admission period, standardized meals were provided. Participants in the reference treatment received a snack (bread and a drink) at around 4 pm. All participants were discharged on Day 3 or Day 11 after 48 h blood samples were collected after dosing. After discharge, participants visited the outpatient clinic for blood sample collection until 72 h after dosing. Throughout the entire study period, alcohol, smoking, heavy exercise, and other drugs were not allowed, except concomitant drug(s) approved by the investigator. The safety was assessed based on adverse events (AEs), vital signs, clinical laboratory evaluations, and physical examination throughout the study period.

Blood sample collection and bioanalysis of cilostazol and itsmetabolites

For the PK analysis, blood samples (6 mL) were collected. Time points for the reference drug were: predose (0 h, just before first tablet administration), 1, 2, 3, 4, 5, 8, 12 (just before second tablet administration), 13, 14, 15, 16, 17, 20, 24, 36, 48, 60, and 72 h postdose. Time points for the test drug were: predose (0 h), 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 h post-dose. Blood was collected into heparinized tubes and allowed to stand for 30 min. Each blood sample was then centrifuged for 10 min at 1910 ×g at 4°C, and two aliquots of 1.5 mL plasma were transferred into Eppendorf tubes and frozen and stored at –70°C until analysis.

Plasma cilostazol, OPC-13015, and OPC-13213 concentrations were determined using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Briefly, 300 μL plasma and 100 μL of the internal standard sample (azelastine; 50 ng/mL acetonitrile) were added to 400 μL of acetonitrile. The mixture was then vortexed for 20 s and centrifuged for 10 min at 21,913 g. An aliquot of the upper organic layer was injected into the HPLC-MS/MS system (HPLC system: HP 1200 [Agilent, Santa Clara, CA, US]; MS/MS system:

Agilent 6410A [Agilent, Waldbronn, Germany]). The column used was an Eclipse XDB-C18 (3.0 mm × 75 mm; 3.5 μm), and the mobile phase consisted of 0.2% formic acid in water: acetonitrile (39:61 v/v) maintained at 0.27 mL/min. The targets were detected using a multiple reaction monitoring (MRM) method with positive electrospray ionization, and the MS transitions were 370.4/288.3 (cilostazol), 368.4/286.3 (OPC-13015), and 386.4/288.3 (OPC-13013), respectively.

The calibration curve for cilostazol was linear over the range 10–2,000 ng/mL (r^2 > 0.99) with intraday accuracy: 96.9–111.8%; precision: 3.0–4.5%; interday accuracy: 102.2–112.7%; and precision: 5.7–8.2%. The calibration curve for OPC-13015 was linear over the range 2–500 ng/mL (r^2 > 0.99) with intraday

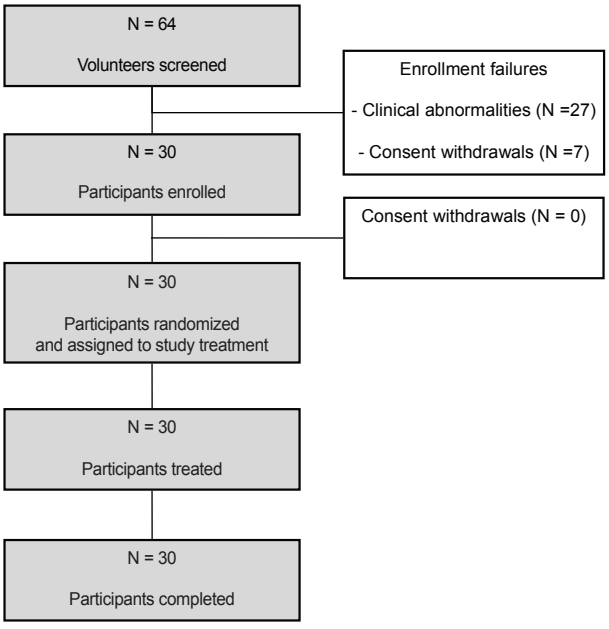

Figure 1. Disposition of the study participants.

Table 1. Demographic characteristics of the study participants

		Group A (n=15)	Group B (n=15)	Total (n = 30)	P
Age (years)		22.9 ± 2.0	23.9 ±2.1	23.4 ± 2	0.188*
Weight (kg)		68.7 ± 7.1	66.9 ± 6.9	67.7 ± 6.8	0.471*
Height (cm)		176.5 ± 5.3	174.0 ± 4.5	175.2 ± 4.9	0.183*
Drinking‡	Yes	8	8	16	> 0.999§
	No	7	7	14	
Smoking‡	Yes	7	8	15	> 0.999§
	No	8	7	15	
Caffeine‡	Yes	4	9	13	0.139§
	No	11	6	17	

Values are presented as mean ± SD; *Mann–Whitney U test. †t test. §Chi-square test

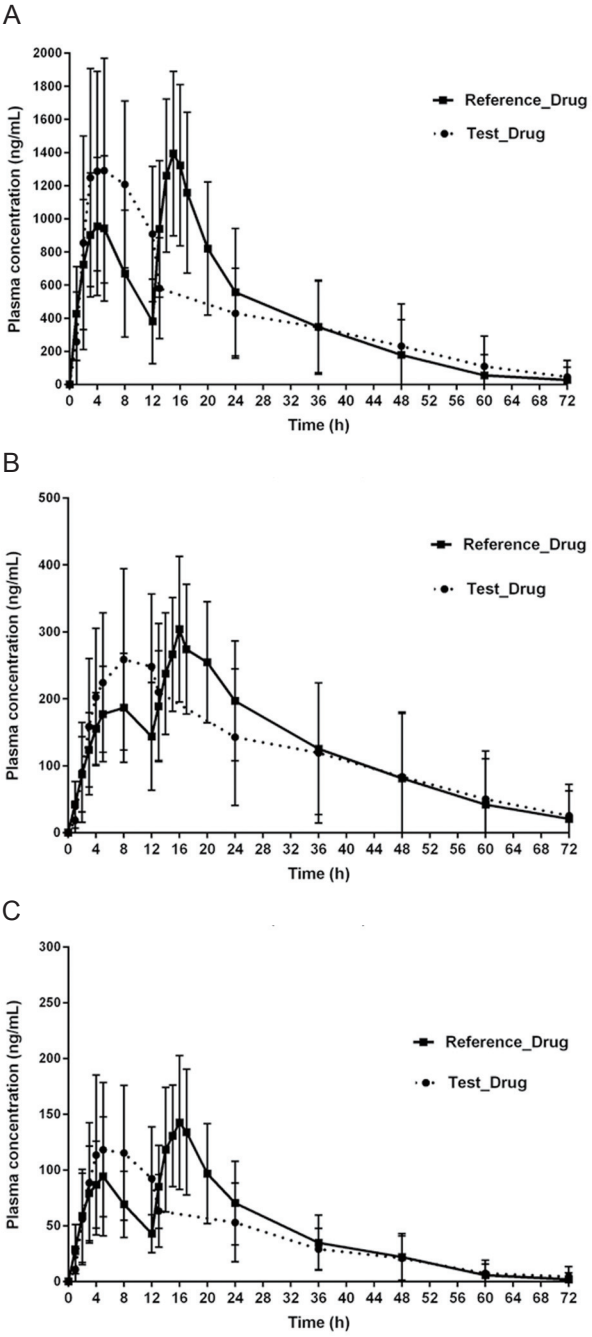

Figure 2. Mean plasma concentration–time profiles of cilostazol (A), OPC13015(3,4-dehydrocilostazol) (B) and OPC13213 (4′-trans-hydroxycilostazol) (C) after oral administration of a single tablet of cilostazol CR 200 mg or two tablets of cilostazol IR 100 mg in healthy Korean male study participants (n = 30). The error bars represent standard deviation. *Reference drug: cilostazol 100 mg IR two tablets, test drug: cilostazol 200 mg CR one tablet.

Table 2. Summary of pharmacokinetic parameters after a single oral administration of the two formulations

Parameters	Cilostazol CR (n = 30)	Cilostazol IR (n = 30)	P
Cilostazol			
C_{max} (ng/ml)	1414.6 (49.3)	1413.1 (35.2)	0.993
	[335.9 to 3097.7]	[420.4 to 2557.4]	
AUC_{last} (ng·h/ml)	23928.7 (65.9)	25312.0 (62.6)	0.528
	[9898.6 to 75046.5]	[6473.8 to 70296.3]	
AUC_{inf} (ng·h/ml)	28232.8 (69.2)	28606.6 (60.6)	0.886
	[13789.1 to 91534.3]	[10160.4 to 79973.5]	
T_{max}* (h)	4.0 [2.0 to 8.0]	15 [2.0 to 24.0]	-
$t_{1/2}$ (h)	15.7 (58.4)	10.6 (68.5)	0.017
	[6.1 to 47.6]	[3.2 to 38.1]	
OPC-13015			
C_{max} (ng/ml)	261.1 (52.5)	290.2 (33.2)	0.370
	[94.9 to 736.6]	[86.9 to 497.1]	
AUC_{last} (ng·h/mL)	6968.8 (82.3)	7630.3 (60.9)	0.317
	[2991.7 to 27186.7]	[2695.0 to 22252.9]	
AUCinf (ng·h/mL)	7348.6 (97.3)	7890.6 (72.0)	0.435
	[3130.4 to 31866.9]	[2846.0 to 28462.5]	
T_{max}* (h)	6.0 [3.0 to 36.0]	16 [15.0 to 36.0]	
$t_{1/2}$ (h)	10.3 (90.1)	8.3 (64.6)	0.052
	[5.2 to 45.0]	[4.7 to 23.9]	
OPC-13213			
C_{max} (ng/mL)	121.3 (57.6)	147.6 (43.2)	0.046
	[30.6 to 326.4]	[76.8 to 349.6]	
AUC_{last} (ng·h/mL)	2412.6 (53.0)	2964.0 (48.1)	0.007
	[996.1 to 5552.8]	[1636.1 to 7767.6]	
AUC_{inf} (ng·h/mL)	2909.3 (52.8)	3183.4 (46.9)	0.260
	[1418.3 to 6648.8]	[1759.6 to 7832.2]	
T_{max}* (h)	5.0 [3.0 to 8.0]	16.0 [3.0 to 24.0]	-
$t_{1/2}$ (h)	15.6 (112.0)	10.5 (4.6)	0.012
	[6.2 to 92.7]	[4.7 to 22.7]	

Values are presented as the geometric mean (CV%) [min to max]. *Median [min to max]. Cmax: Maximum plasma concentration. AUC_{last}: Area under the plasma concentration–time curve to the last sampling time. AUC_{inf}: Area under the plasma concentration–time curve to infinity. T_{max}: Time to C_{max}. $t_{1/2}$: Terminal half-life.

accuracy: 87.5–108.0%; precision: 3.0–8.7%; interday accuracy: 92.0–107.2%; and precision: 4.7–13.1%. The calibration curve for OPC-13013 was linear over the range 5–1,000 ng/mL (r^2 > 0.99) with intraday accuracy: 86.9–107.1%; precision: 5.8–11.7%; interday accuracy: 96.8–100.6%; and precision: 6.4–12.2%.

Pharmacokinetic analysis

The individual plasma concentration–time curves were constructed using Prism 6 for Windows (GraphPad Software, La Jolla, CA, USA). The area under the plasma concentration–time curve from 0 to the last measurable concentration sampling time (AUC_{last}) was calculated by noncompartmental methods using WinNonlin version 5.3 (Pharsight Co., Princeton, NJ, USA). The peak concentration (C_{max}) and the time to peak plasma concentration after administration (t_{max}) values were directly obtained from the plasma concentration–time curves. AUC_{last} was calculated using a linear trapezoidal method by increasing the period, and log–linear trapezoidal summation in the decreasing period. From the terminal slope, linear regression was used to estimate the elimination rate constants and to obtain the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{inf}), and the half-life ($t_1/_{2\beta}$) was obtained by calculating the ln(2)/terminal elimination constant (λ_z) at the terminal phase of the log–linear plot of the concentration–time curve. To compare the PK profiles of cilostazol CR and cilostazol IR, the log-transformed individual C_{max} and AUC_{last} values were analyzed using a mixed-effects analysis of variance. The treatment effects are shown as the geometric mean ratio (test/reference; cilostazol CR/ cilostazol IR) and 90% confidence intervals (90% CI).

Safety assessment

Throughout the study, safety was assessed based on adverse events (AEs), concomitant medications, physical examination, vital signs, clinical laboratory evaluation, and electrocardiograms. The frequency and severity of adverse events in the cilostazol IR and CR groups were compared using a chi-square or Fisher exact test.

Statistical analysis

The statistical analysis was performed by using SAS (version 9.3, SAS Institute Inc., Cary, NC, USA). The plasma cilostazol, OPC-13015, and OPC-13213 measurements that were below the limit of quantification after drug administration were assigned values of zero if collected before C_{max} and were treated as missing values if collected after C_{max}. Descriptive statistics, including mean ± SD, were used to summarize the PK data for the two formulations. Formulation, sequence, and period were used as fixed effects, and a participant nested within the sequence was used as a random effect. T_{max} was compared between the formulations using a signed rank test, and a distribution-free 90% CI for median difference was estimated using a Hodges–Lehmann estimator. The two tablet formulations

Table 3. Bioequivalence assessment of pharmacokinetic parameters

PK parameter	Geometric mean ratio (Cilostazol CR/cilostazol IR)	
	Point estimate	90% Confidence interval
Cilostazol		
C_{max} (ng/ml)	1.001	0.822 to 1.220
AUC_{last} (ng·h/ml)	0.945	0.814 to 1.098
AUC_{inf} (ng·h/ml)	0.987	0.845 to 1.152
OPC-13015		
C_{max} (ng/ml)	0.873	0.717 to 1.063
AUC_{last} (ng·h/ml)	0.907	0.786 to 1.047
AUC_{inf} (ng·h/ml)	0.923	0.795 to 1.071
OPC-13213		
C_{max} (ng/mL)	0.831	0.713 to 0.969
AUC_{last} (ng·h/ml)	0.818	0.728 to 0.919
AUC_{inf} (ng·h/ml)	0.902	0.788 to 1.032

C_{max}: Maximum plasma concentration. AUC_{last}: Area under the plasma concentration–time curve to the last sampling time. AUC_{inf}: Area under the plasma concentration–time curve to infinity.

would be considered bioequivalent if the 90% CIs for GMR were within the range of 0.8 to 1.25.

Results

Participants

A total of 64 volunteers underwent screening tests, and 32 were found to be eligible to participate in the study. The 32 eligible volunteers were enrolled, but two withdrew their consent before randomization. Therefore, 30 participants were randomized and included in the safety and pharmacokinetic evaluations. These 30 participants were administered the study drug during one of the two periods and completed the study (Fig. 1).

Participant demographics including age, height, and weight, and alcohol, nicotine, and caffeine consumption are presented in Table 1 and were not significantly different between the two groups.

Pharmacokinetic analysis

PK parameters were determined using the cilostazol, OPC-13015, and OPC-13213 concentration data obtained from the 30 participants who completed the study. The plasma concentration–time profiles for cilostazol, OPC-13015 and OPC-13213 are shown in Figure 2. The geometric mean (standard deviation, SD) C_{max} value for cilostazol, OPC-13015, and OPC-13213 were 1413.1 (35.2), 290.2 (33.2), and 147.6 (43.2) ng/mL after the two tablets of cilostazol IR, while those for cilostazol CR after the single tablet were 1414.6 (49.3), 261.1 (52.5) and 121.3 (57.6) ng/mL. The geometric means (SD) AUC_{last} for cilostazol, OPC-13015, and OPC-13213 were 25312.0 (62.6), 7630.3 (60.9) and 2964.0 (48.1) ng/mL in the case of cilostazol IR, while those for cilostazol CR were 23928.7 (65.9), 6968.8 (82.3), and 2412.6 (53.0) ng/mL. The median (min to max) T_{max} for cilostazol, OPC-13015, and OPC-13213 after the two tablets of cilostazol IR were 15.0 (2.0 to 24.0), 16.0 (15.0 to 36.0) and 16.0 (3.0 to 24.0), while those for cilostazol CR were 4.0 (2.0 to 8.0), 6.0 (3.0 to 36.0), and 5.0 (3.0 to 8.0) h.

In the comparison of cilostazol PKs, the GMR (test/reference) of the C_{max} and AUC_{last} were 1.001, 0.945, and the 90% CI were 0.822 to 1.220 and 0.814 to 1.098, respectively. All PK parameters were within the range of 0.8 to 1.25, which is the criterion for bioequivalence (Table 3). In the comparison of OPC-13015 PK, the GMR (test/reference) of the C_{max} and AUC_{last} were 0.873 and 0.907, and the 90% CI were 0.717 to 1.063 and 0.786 to 1.047, respectively. In the comparison of OPC-13213 PK, the GMR (test/reference) of the C_{max} and AUC_{last} were 0.831, 0.818 and the 90% CI were 0.713 to 0.969 and 0.728 to 0.919, respectively.

Safety evaluation

No serious AEs occurred in this study, and no unexpected AEs that could have influenced the outcome of the study were observed. AEs that were considered to be 'certainly' related to the test or reference drugs were headache, sinus tachycardia, hypotension, and dizziness, and AEs that were considered to be 'unlikely' to be related to the drugs were myalgia and sore throat. Vital signs including blood pressure, pulse rate, body temperature, and the physical examination results for the study participants showed no clinically important changes.

Discussion

This study was conducted to evaluate the PK characteristics and tolerability of cilostazol CR and IR after single oral dose of healthy Korean male participants. To our knowledge, this is the first study using a single-dosing PK design, and if possible, a multiple-dosing design study will be conducted to develop the CR formulation. In the present study, we showed that the PK characteristics of cilostazol were similar between the two drug formulations, and those of its metabolites (OPC-13015 and 13213) were not similar. Although the metabolite PKs of the two drug formulations are different, the similarity of the parent drug PK provided evidence of good bioequivalence of the two drug formulations. The most recent guidance states that the use of the parent compound for bioequivalence assessment relies on the fact that the concentration–time profile for the parent drug is a more sensitive method by which to detect differences in formulation performance than the profile of the metabolites. The PKs of metabolites are required in the following cases: (1) if the concentration of the parent compound is low, or (2) if the concentration of the parent compound is unstable or if its half-life is short.[8,9,10] After a single 200 mg tablet of cilostazol CR,

the 90% CIs for GMRs of C_{max} and AUC_{last} satisfied commonly accepted bioequivalence criteria. C_{max} of OPC-13015 and OPC-13213 were 13% and 17% lower, and AUClast of OPC-13015 and OPC-13213 were 9% and 18% lower, respectively, compared with two 100 mg tablets of cilostazol IR. Our PK results are consistent with those of previous clinical studies.[11,12] The terminal half-lives of the CR and IR formulations were 15.7 h and 10.6 h, respectively. These indicated that the CR formulation has extended cilostazol release properties. These PK properties enable the frequency of dosing to be reduced, which has been shown to improve patient compliance. The pharmacodynamic effects were shown to be well correlated with the PK profile.[13] Therefore, the cilostazol CR formulation would be expected to provide effects in patients similar to those of the cilostazol IR formulation.

In conclusion, this study found that the PK values for cilostazol CR and IR were within the commonly accepted bioequivalence range of 0.8 to 1.25. Both formulations of cilostazol were well tolerated.

Acknowledgments

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1063). This work was also supported by a research fund of Chungnam National University and supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2014R1A6A1029617).

Conflict of interest

All authors declare that there are no conflicts of interest.

References

1. Sorkin EM, Markham A. Cilostazol. Drugs Aging 1999;14:63-71.
2. Horie N, Kaminogo M, Izumo T, Hayashi K, Tsujino A, Nagata I. Cilostazol may prevent cardioembolic stroke in patients undergoing antiplatelet therapy. Neurol Res 2015;37:619-623. doi: 10.1179/1743132815Y.0000000021.
3. Liu JS, Chuang TJ, Chen JH, Lee CH, Hsieh CH, Lin TK, et al. Cilostazol attenuates the severity of peripheral arterial occlusive disease in patients with type 2 diabetes: the role of plasma soluble receptor for advanced glycation end-products. Endocrine 2015;49:703-710. doi: 10.1007/s12020-015-0545-6.
4. Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. Pharmacology 1988;36:313-320.
5. Dawson DL, Cutler BS, Meissner MH, Strandness DE, Jr. Cilostazol has beneficial effects in treatment of intermittent claudication. Results from a multicenter, randomized, prospective, double-blind trial. Circulation 1998;98:678-686.
6. Dawson DL, Cutler BS, Hiatt WR, Hobson RW 2nd, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J med Med 2000;109:523-530.
7. Shin KH, Yoon G, Yoon IS, Park JW. Preparation and evaluation of oral controlled-release cilostazol formulation: pharmacokinetics and antithrombotic efficacy in dogs and healthy male Korean participants. J Pharm Pharmacol. 2014;66:961-974. doi: 10.1111/jphp.12227.
8. Karalis V, Macheras P. Examining the role of metabolites in bioequivalence assessment. J Pharm Pharm Sci 2010;13:198-217.
9. Srinivas NR. Considerations for metabolite pharmacokinetic data in bioavailability/bioequivalence assessments. Overview of the recent trends. Arzneimittelforschung 2009;59:155-165. doi: 10.1055/s-0031-1296380.
10. Jackson AJ, Robbie G, Marroum P. Metabolites and bioequivalence: past and present. Clin Pharmacokinet 2004;43:655-672.
11. Kim HS, Kim GY, Yeo CW, Oh MK, Ghim JL, Shon JH, et al. The effect of Ginkgo biloba extracts on the pharmacokinetics and pharmacodynamics of cilostazol and its active metabolites in healthy Korean subjects. Br J Clin Pharmacol 2014;77:821-830. doi: 10.1111/bcp.12236.
12. Kim YH, Ghim JL, Jung JA, Cho SH, Choe S, Choi HY, et al. Pharmacokinetic comparison of sustained- and immediate-release formulations of cilostazol after multiple oral doses in fed healthy male Korean volunteers. Drug Des Devel Ther 2015;9:3571-3577. doi: 10.2147/DDDT.S86845.
13. Woo SK, Kang WK, Kwon KI. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiov ascular effects of cilostazol in healthy humans. Clin Pharmacol Ther 2002;71:246-252.