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Bioequivalence Assessment of Domperidone Maleate Tablets in Healthy Korean Volunteers

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Abstract–The bioequivalence of two tablet formulations of 12.72 mg domperidone maleate (Sinil "Perinal®" tablets vs. Janssen Korea "Motilium-M®" tablets) was assessed in healthy Korean volunteers after oral administration in a randomized crossover study. Blood samples were collected at specified time intervals, and plasma concentration was measured as the amount of domperidone base using a validated HPLC method. The pharmacokinetic parameters of $AUC_{0\rightarrow48}$, C_{max}, T_{max} and $t_{1/2}$ were determined from plasma concentration-time profile of two formulations. Any significant statistical differences were not observed between these two formulations. On the evaluation of bioequivalence according to Korea Food and Drug Administration Guideline, 90% confidence limits after logarithmic transformation fell within the acceptable range (log 0.8~log 1.25). Based on these data, it can be concluded that two domperidone maleate tablets showed comparable pharmacokinetic profiles, which means that the Sinil "Perinal®" tablet is bioequivalent to the Janssen Korea "Motilium-M®".

Keywords □ domperidone, bioequivalence, pharmacokinetics, HPLC, Perinal®, Motilium-M®

Domperidone, 5-chloro-1-{1-[3-(2,3-dihydro-2-oxo-1*H*-benzmidazol-1-yl)-propyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one, is a peripheral dopamine D_2 receptor antagonist, which has the properties of preventing nausea as well as vomiting, and of prompting gastrointestinal motility (Laduron and Leysen, 1979; Brogden *et al.*, 1982; Champion *et al.*, 1986; Champion, 1988). Thus domperidone has been widely used for the treatment of functional gastrointestinal disorders including dyspepsia, gastroesopharyngeal reflux, nausea and vomiting. Moreover, domperidone is co-administered with other medications such as anticancer agents or anti-Parkinson agents, in order to prevent the common side effects (Mitchelson, 1992; MacGregor, 2001).

Domperidone is available as tablets, effervescent granule or suspension for oral administration. A formulation of rectal suppositories is also supplied for children weighed over 5 kg (Parfitt, 1999). Domperidone maleate used in tablet preparations has been developed for the short-term treatment of nausea and vomiting in various etiologies, including cancer therapy and Parkinsonism therapy.

The systemic bioavailability of oral domperidone is low, at around 13~17% (Heykants *et al.*, 1981b), probably not due to its poor absorption in gastrointestinal tract, but due to the first-pass hepatic and gut metabolism (Heykants *et al.*, 1981a). Domperidone is mainly metabolized by hyroxylation and oxidative *N*-alkylation, yielding hydroxydomperidone and 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-propionic acid, respectively (Meuldermans *et al.*, 1981). Of the orally administered domperidone, 31% of dose is excreted through urine and 66% through feces, but only 1.4% of urinary excretion and less than 10% of fecal excretion remain as unchanged form (Meuldermans *et al.*, 1981).

The determination of domperidone in plasma has been conducted by radioimmunoassy (Huang *et al.*, 1986), high-performance liquid chromatography (HPLC) (Yamamoto *et al.*, 1998, Kobylinska and Kobylinska, 2000), and liquid chromatography coupled with mass spectrometry (LC-MS) (Zavitsanos *et al.*, 1999; Smit *et al.*, 2002; Wu *et al.*, 2002). Among them, HPLC analysis of domperidone is more popular because of its easy operation, high sensitivity and accuracy, and reproducibility. Yamamoto *et al.* (1998) firstly applied the fluorescence detector in HPLC system for the determination of domperidone in rat plasma. In order to increase the sensitivity, Kobylinska and Kobylinska (2000) introduced simple solid-phase extraction

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(SPE) system prior to analysis of domperidone in human plasma.

The first pharmacokinetc analysis for the healthy volunteers were evaluated by radioimmunoassay, who were received oral administration of 2 tablets of 10 mg domperidone base, 2 tablets of 12.72 mg domperidone maleate, or 20 mg of domperidone solution (4 ml of 5 mg/ml), and it was observed that all 3 groups showed the similar pharmacokinetic patterns (Huang *et al.*, 1986). In another study using HPLC, the healthy Polish volunteers administered 2 tablets of 12.72 mg domperidone maleate orally also showed the similar pharmacokinetic parameters (Kobylinska and Kobylinska, 2000). In recent study by LC-MS analysis, Wu *et al.* (2002) reported similar but slightly high pharmacokinetic values in healthy Chinese volunteers.

The purpose of this work was to compare the bioavailability (rate and extent of absorption) of generic domperidone maleate formulation (Sinil "Perinal®" tablets) to that of the reference formulation (Janssen Korea "Motilium-M®" tablets), both of which contain 12.72 mg of domperidone maleate. The concentrations of domperidone base in human plasma were determined by HPLC coupled with fluorescence detector after pretreatment with SPE cartridge.

MATERIALS AND METHODS

Materials

Sinil "Perinal®" tablets containing 12.72 mg of domperidone maleate (10 mg as domperidone base) were provided by Sinil Pharmaceutical Co. Ltd. (Seoul, Korea). Those white round tablets were produced on November 8, 2001 under the batch number of 111091. As a reference formulation, Janssen Korea "Motilium-M®" tablets (12.72 mg of domperidone maleate) were used, which were prepared by Janssen Korea Ltd. (Seoul, Korea) under the batch number of 6841 on April 19, 2001. Authentic domperidone (purity; >99%) were kindly supplied from Shinpoong Pharmaceutical Co. Ltd. (Seoul, Korea), and cisapride (purity; 100%) from Hanmi Fine Chemical. Co., Ltd. (Siheung, Korea). Methanol as HPLC grade was purchased from J. T. Baker (NJ, USA), and other reagents used in this work were of the anlytical grade.

Study subjects

After approval of pre-planned proposal for the study by Korea Food and Drug Administration (KFDA, Seoul, Korea), volunteers who submitted the agreement to attend in this project were medically examined and 16 healthy volunteers including 2 females were selected by a medical doctor in Yeungnam University Medical Center (Daegu, Korea), based on clinical examination including seropathological (hemoglobin, hematocrit, WBC, platelet, differential counting of WBC), serochemical (blood urea nitrogen, creatinine, total protein, albumin, serum glutamate-oxaloacetate transaminase (sGOT), serum glutamate-pyruvate transaminase (sGPT), total bilirubin, cholesterol, glucose fasting, alkaline phosphatase), and urological (specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC) data. The subjects were instructed not to take any medicine for at least 1 week prior to and during the study period. Neither beverages nor caffeine was allowed during the study. Informed consent was filled up by the subjects after explanation of the nature and aims of the work. They were accommodated to the same place one day before blood collection, and fasted overnight before administration of the tablets.

Oral administration and blood sampling

A three-way gauge set was established on the forearm vein of the volunteers, and 8 ml of blood for blank was collected. According to the prescription directed by the doctor, two tablets (20 mg as domperidone base) were orally taken to the designated group at random design (8 volunteers each group) with 240 ml of water. One group received the test tablets, and the other for reference. Blood sampling of each groups was undertaken at 12 points of 0.33, 0.67, 1, 1.5, 2, 4, 6, 9, 12, 24, 36, and 48 hr after administration, with the time interval of 2 min to consider blood collection. Blood samples were withdrawn into heparin-treated Vacutainer tubes (Becton Dikinson, NJ, USA), and centrifuged to obtain plasma at 4°C. The obtained plasma was stored at -70°C until analysis. No food was allowed until 4 hr after administration, but the same lunch and dinner were provided to volunteers according to a time schedule. These two groups were made to take again the formulations by the 2×2 Latin square crossover design after they spent a wash-out period for two weeks.

HPLC analysis

The concentration of domperidone base in plasma was determined by using a HPLC system (Model LC-10AT$_{vp}$, Shimadzu Corporation, Japan) equipped with a solvent delivery system (Model SCL-10AD$_{vp}$) and an auto sampler (Model SIL-10A$_{vp}$). The separation of domperidone was performed through a Shimpack VP-ODS column (No. 228-34937-92; I.D., 250×4.6 mm; 5 μm particles) with a flow rate of 1.0 ml/min of methanol-water-triethylamine-acetic acid (45:55:0.02: 0.3, v/

v%), and the amount of domperidone was detected by RF-$10A_{XL}$ fluorescence detector operated at 282 nm for excitation and at 326 nm for emission. All the data were processed and analyzed using Class-VP5.0 software program. The sample of 20 μl was applied to the HPLC system, and the amount of domperidone in sample was calculated from the area ratio of the peak of domperidone to that of cisapride (internal standard) using calibration curve.

Pre-treatment of plasma samples

Before HPLC analysis, the plasma samples were pre-treated according to the procedure of Kobylinska and Kobylinska (2000) with some modification. To 1 ml aliquot of thawed plasma in a 15 ml centrifuge tube, 20 ng (4 μg/ml in methanol, 50 μl) of cisapride as an internal standard, 30 μl of 0.1 M sodium hydroxide solution, and 5 ml of chloroform were added, and tube was shaken vigorously for 15 min. After centrifuging at 3,000 rpm for 5 min, 4 ml of organic phase was withdrawn into a new tube. To this, 2.5 ml of 0.01 M hydrochloric acid was added, and 2 ml of aquous phase was taken after vigorous shaking for 10 min and centrifuging at 3,000 rpm for 5 min. The resulting sample was passed through Strata^{TM} CN cartridge (3 ml; Phenomenex, CA, USA) already washed with 2 ml of water and 1 ml of acetone, and then eluted with 1 ml of methanol-triethylamine-acetic acid (100:0.03:0.3, v/v). The remaining solution in a cartridge was recovered by centrifuging at 3,000 rpm for 1 min. The collected eluent was evaporated to dryness under nitrogen atmosphere at 50°C, and the residue was dissolved in 200 μl of HPLC mobile phase by vortexing for 10 sec. For calibration curve, blank plasma having 2, 5, 10, 25, 50, and 100 ng/ml of domperidone was prepared and analyzed by the same procedure.

Pharmacokinetic analysis and statistics

Pharmacokinetic parameters were determined from time profile of domperidone concentrations in plasma by non-compartmental analysis. The highest concentration (C_{max}) and the time to reach the highest concentration (T_{max}) were read directly from the time-plasma concentration curves. The area under the curve of time-plasma concentrations of domperidone until final sampling time ($AUC_{0\to48}$) was calculated by using BA Calc 2002 software (Seoul National University, Seoul, Korea). Mean elimination half-life ($t_{1/2}$) and mean elimination constant (K_{el}) were evaluated by WinNonlin program (ver. 1.1) of Scientific Consulting Inc. (NC, USA). All the data were presented as mean standard deviation. K-BE Test 2002 software (KFDA and Seoul National University, Seoul, Korea) was also used for the determination of bioavailability ratio, minimum detection difference, F value and 90% confidence limit (Lee *et al.*, 2002). Two formulations are considered to be bioequivalent when 90% confidence limits of logarithmically transformed C_{max} and $AUC_{0\to48}$ are ranged between log 0.8 and log 1.25 according to the KFDA guideline (KFDA, 2001).

RESULTS AND DISCUSSION

Validation of Analytical method

Before the analysis of domperidone concentration in human plasma, the analytical method by HPLC was validated. Retention times of domperidone and cisapride in HPLC chromatogram (n = 7) were about 10.7 ± 0.6 and 20.4 ± 1.8 min, respectively (Fig. 1). Detection limit of domperidone obtained from 1 ml of plasma by HPLC method was 2 ng/ml when the ratio of signal to noise was 50. Calibration curve showed good linearity at concentrations from 2 to 100 ng/ml of domperidone

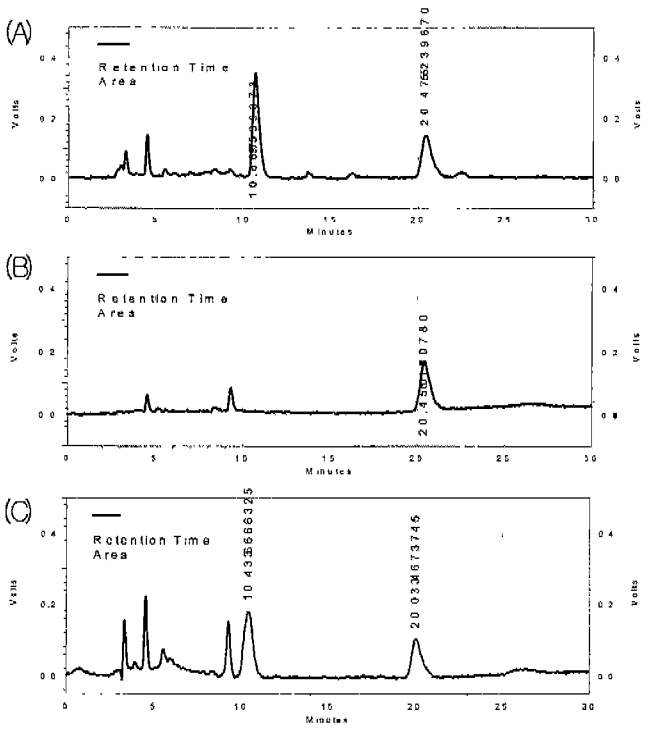

Fig. 1. The HPLC chromatograms obtained from (A) standard of domperidone (50 ng/ml) and internal standard cisapride (20 ng/ml), (B) blank plasma spiked with internal standard, and (C) plasma sample at 1 hr after oral administration of two 12.72 mg domperidone maleate tablets to a human volunteer. Retention times of domperidone (peak 1) and cisapride (peak 2) were around 10.7 and 20.4 min, respectively.

Table I. Intra-day and inter-day precision and accuracy for the determination of domperidone in the plasma.

Concentration of domperidone (ng/ml)	Intra-day precision (CV%) n=5	Inter-day precision (CV%) n=5	Accuracy (%)
2	0.1115 ± 0.0065 (5.78)	0.1123 ± 0.0071 (6.36)	87.44
10	0.3705 ± 0.0336 (9.07)	0.4337 ± 0.0110 (2.54)	99.60
20	0.7017 ± 0.0465 (6.63)	0.7819 ± 0.0159 (2.03)	97.86
50	1.6218 ± 0.0465 (2.87)	1.8157 ± 0.0821 (4.52)	94.43
100	3.5957 ± 0.0345 (0.96)	3.8451 ± 0.2938 (7.64)	103.86

(y=0.03534x+0.05010, R^2=0.9991) (Fig. 2). Coefficient of variation (CV%) for intra-day and inter-day precisions were 0.96~9.07% and 2.03~7.64%, respectively. Accuracy was between 90~110%, except 2 ng/ml sample of domperidone at lower detection limit, as shown in Table I.

Pharmacokinetic Analysis

All 16 volunteers have participated in the bioequivalent assessment experiment of domperidone maleate tablets. The mean age of the volunteers was 23.6 ± 1.5 years, ranging from 21 to 25 years. The mean body weight was 64.7 ± 8.6 kg with the ranges between 50 and 83 kg, and the height of the volunteers was ranged from 163 to 180 cm with the mean value of 170.9 ± 4.5 cm, as shown in Table II. The seropathological, serochemical and urological data of the volunteers were in the range of normal value, indicating that no subjects have hepatic, renal or hematological disorder or malfunction.

Oral dosage of domperidone maleate was decided as 25.44 mg (2 tablets), which is equivalent with 20 mg of domperidone base, following the previous pharmacokinetic studies (Huang *et al.*, 1986; Kobylinska and Kobylinska, 2000). The plasma concentrations of domperidone during 48 hrs after oral adminstration were determined by HPLC analytic method, and the time-plasma concentration profiles of domperidone for ref-

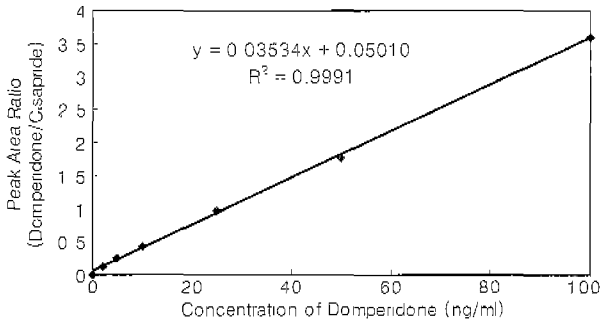

Fig. 2. Calibration curve for domperidone in plasma sample. The amount of domperidone was expressed as the peak area ratio to that of cisapride (internal standard).

Table II. Physical and pharmacokinetic parameters after administration of domperidone formulations (two tablets of 12.72 mg domperidone maleate) to healthy Korean volunteers participated in the bioequivalence study

Subject	Sex	Age (yrs)	Weight (Kg)	Height (cm)	Janssen Korea "Motilium-M®"			Sinil "Perinal®"		
					$AUC_{0\to48}$ (ng · hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0\to48}$ (ng · hr/ml)	C_{max} (ng/ml)	T_{max} (hr)
A1	M	25	60	170	176.14	50.00	1.00	89.06	37.59	0.67
A2	M	24	60	167	123.31	37.14	1.00	181.09	65.25	0.67
A3	M	25	72	172	137.08	38.94	1.00	270.05	49.10	1.00
A4	M	25	65	174	154.53	68.76	0.67	159.78	48.91	0.67
A5	M	25	68	170	102.33	34.94	0.67	106.90	27.44	1.00
A6	M	23	57	167	264.03	61.62	0.33	182.64	58.12	1.00
A7	F	21	65	163	192.70	55.46	1.00	134.70	49.12	1.00
A8	F	21	50	163	111.40	31.76	0.67	112.81	49.34	1.00
B1	M	25	83	180	72.79	40.27	1.00	97.36	39.19	0.67
B2	M	24	76	174	41.08	32.57	0.67	69.72	20.32	0.67
B3	M	24	60	169	97.60	52.95	0.67	101.97	70.01	0.33
B4	M	21	74	176	113.00	35.63	0.67	95.17	42.68	0.67
B5	M	25	67	170	123.36	58.02	0.67	110.98	58.20	0.33
B6	M	23	60	172	55.43	17.80	0.67	69.86	20.08	0.67
B7	M	23	53	175	135.06	68.49	0.67	182.23	57.02	0.67
B8	M	24	65	172	95.02	46.65	0.67	92.04	34.05	0.67
Mean ± S.D.		23.6 ± 1.5	64.7 ± 8.6	170.9 ± 4.5	138.42 ± 56.26	45.69 ± 14.46	0.75 ± 0.19	145.19 ± 55.08	45.40 ± 14.93	0.73 ± 0.22

erence formulation (Janssen Korea "Motilium-M®" tablet) and test formulation (Sinil "Perinal®" tablet) were obtained as seen in Fig. 3. From this, the principal pharmacokinetic parameters were calculated by using BA Calc 2002 software, as summarized in Table II. Any significant statistical differences in $AUC_{0\rightarrow48}$, C_{max}, and T_{max} values between the test and the reference formulations were not found. The mean $AUC_{0\rightarrow48}$ values were calculated as 138.42 ± 56.26 ng · hr/ml for the reference and 145.19 ± 55.08 ng · hr/ml for the test formulation. The mean C_{max} values for the reference and test formulations were 45.75 ± 14.53 and 45.40 ± 14.93 ng/ml, respectively. And the mean T_{max} values were 0.75 ± 0.19 hr for the reference formulation and 0.73 ± 0.22 hr for the test formulation.

The mean elimination half-life ($t_{1/2}$) and mean elimination constant (K_{el}) of domperidone malcate tablets orally administered were also obtained from the time-plasma concentration profile as 4.58 ± 1.76 hr and 0.19 ± 0.11 hr^{-1} for reference, and as 4.86 ± 1.57 hr and 0.15 ± 0.04 hr^{-1} for test, respectively (Table III). All the pharmacokinetic parameters were similar with the data obtained by the previous researchers' (Huang *et al.*, 1986; Kobylinska and Kobylinska, 2000; Wu *et al.*, 2002). However, it was interesting that the AUC_{last} and C_{max} values obtained in this experiment were somewhat higher than the case of Western volunteers, as likely as Chinese case reported by Wu *et al.* (2002). Considering that low systemic bioavailability of oral domperidone has been known in Western subjects (Heykants *et al.*, 1981a), it can be assumed that Oriental people like Korean or Chinese may have higher bioavailability than Western people.

According to the definition made by Shargel and Yu (1993),

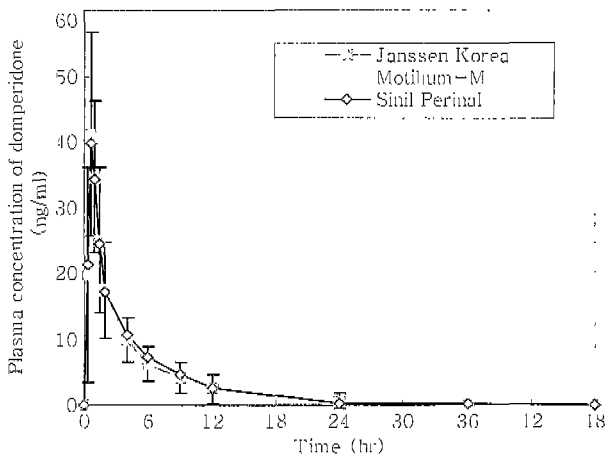

Fig. 3. The plasma concentration of domperidone versus time curves after oral administration of the different formulations of two 12.72 mg domperidone maleate tablets to 16 healthy Korean volunteers. Mean values (± S.D.) for each formulations were represented on the graph.

the biocquivalent drug products are pharmaceutical equivalents having similar bioavailability, which are not significantly different with respect to rate and extent of absorption when given in the same molar dose and studied under similar conditions. In this viewpoint, it can be concluded that Sinil "Perinal®" tablet is pharmacokinetically equivalent with Janssen Korea "Motilium-M®" tablet.

Statistical Analysis for Bioequivalent Assessment

Statistical analysis of variance was also carried out using logarithmically transformed $AUC_{0\rightarrow48}$, C_{max} and T_{max} values (Table IV). Any significant differences between these two formulations were not observed in $AUC_{0\rightarrow48}$ and C_{max} values

Table III. Comparison of pharmacokinetic parameters of domperidone maleate tablets with previous researchers'.

Reference or Formulation	Analytical Method	$AUC_{0\text{-}48}$ (ng · hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (hr^{-1})
Huang *et al.*, 1986	RIA	84.46 ± 19.86	15.04 ± 7.40	1.2 ± 0.5	12.6 ± 6.5	-
Kobylinska and Kobylinska, 2000	HPLC	75.45 ± 24.33	20.67 ± 5.32	0.84 ± 0.36	7.7 ± 3.1	0.11 ± 0.05
Wu *et al.*, 2002	LC-MS	168 ± 72	50 ± 32	0.8 ± 0.7	7.8 ± 1.6	0.09 ± 0.02
This Work						
Janssen Korea "Motilium-M®"	HPLC	138.42 ± 56.26	45.75 ± 14.53	0.75 ± 0.19	4.58 ± 1.76	0.19 ± 0.11
Sinil "Perinal®"	HPLC	145.19 ± 55.08	45.40 ± 14.93	0.73 ± 0.22	4.86 ± 1.57	0.15 ± 0.04

Table IV. Statistics for pharmacokinetic and bioequivalence parameters of domperidone maleate tablets

	$AUC_{0\rightarrow48}$	C_{max}	T_{max}
F value, drug	0.381	0.001	0.178
(Test/Reference) bioavailability ratio	1.056	0.998	0.956
Minimum detection difference (Δ%)	30.54	24.64	37.20
90% Confidence limit, log-transformed (μ_T/μ_R)	$0.90 \le \mu_T/\mu_R \le 1.23$	$0.88 \le \mu_T/\mu_R \le 1.13$	$0.80 \le \mu_T/\mu_R \le 1.15$

All the data were obtained by using K-BE Test 2002 software after transformed logarithmically ($a = 0.05$).

transformed logarithmically. The bioavailability ratio of test formulation to reference formulation in $AUC_{0\rightarrow48}$, C_{max} and T_{max} values were 1.056, 0.998 and 0.956, and the minimum detection difference for $AUC_{0\rightarrow48}$, C_{max} and T_{max} were 30.54%, 24.64% and 37.20%, respectively. And the 90% confidence limits for these parameters transformed logarithmically were located in the range of 0.8 and 1.25, which are satisfied the bioequivalence acceptance criteria described in the KFDA guideline (KFDA, 2001).

All taken together, the statistical comparison of $AUC_{0\rightarrow48}$ and C_{max} indicated no significant differences in two brands of 12.72 mg domperidone maleate tablets. Especially, 90% confidence intervals for $AUC_{0\rightarrow48}$ and C_{max} were satisfied the bioequivalence criteria regulated by KFDA (KFDA, 2001), which were enacted following the regulation of Europe and U.S.A. (EMEA, 2001; FDA, 2001).

Based on all the pharmacokinetic and statistical data, it can be conclude that the Sinil "Perinal®" tablet is bioequivalent to the "Motilium-M®" tablet manufactured by Janssen Korea. If the drug products are demonstrated to be bioequivalent, then the efficacy of these drugs is assumed to be similar, and the generic substitution of two products is possible in medical practice.

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