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Pharmacokinetics of Lansoprazole Enantiomers in Renal Transplant Recipients with CYP2C19 Extensive Metabolizers

三浦 昌朋[*1], 多田 均[*1], 佐藤 滋[*2], 加賀谷英彰[*1],
柳原せい子[*3], 佐々木吉幸[*3], 羽渕 友則[*2], 鈴木 敏夫[*1]

[*1]秋田大学医学部附属病院薬剤部

[*2]秋田大学医学部生殖発達医学講座
泌尿器科学分野

[*3]秋田赤十字病院薬剤部

MASATOMO MIURA[*1], HITOSHI TADA[*1], SHIGERU SATOH[*2], HIDEAKI KAGAYA[*1],
SEIKO YANAGIHARA[*3], YOSHIYUKI SASAKI[*3], TOMONORI HABUCHI[*2],
and TOSHIO SUZUKI[*1]

[*1]Department of Pharmacy, Akita University Hospital

[*2]Department of Urology, Akita University School of Medicine

[*3]Department of Pharmacy, Akita Red Cross Hospital

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〒010-8543 秋田市本道1-1-1 : 1-1-1 Hondo, Akita-shi, 010-8543 Japan

Abstract

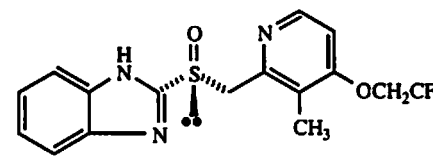
The purpose of this study was to evaluate the pharmacokinetics of lansoprazole enantiomers in renal transplant patients with CYP2C19 normal (extensive) metabolizers receiving tacrolimus. On day 28 after renal transplantation, the mean plasma concentrations of (*R*)-lansoprazole after oral administration of 30 mg racemic lansoprazole were significantly higher than those of the (*S*)-enantiomer, and the *R*/*S* ratios for C_{max} and $AUC_{0\text{-}24}$ of lansoprazole was 4.0±0.4 and 8.0±4.0, respectively. Further, the CL/F and Vd/F values of (*S*)-lansoprazole were 6.8- and 6.3-fold, respectively, greater than those of the (*R*)-enantiomer ($p<0.01$). The pharmacokinetic parameters of both enantiomers of lansoprazole in renal transplant patients receiving tacrolimus found to be in good agreement with previously reported values for healthy Korean subjects who received a single dose. In addition, the effect of tacrolimus on the pharmacokinetics of lansoprazole was not observed.

Key words — Lansoprazole, Tacrolimus, Enantiomer, Pharmacokinetics, CYP2C19 extensive metabolizers

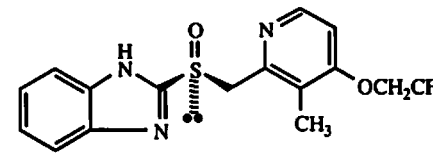
Introduction

Lansoprazole, 2 - [(3 - methyl - 4 - (2,2,2 - trifluoethoxy) - 2 - pyridyl)methyl] sulfinyl - benzimidazole, is one of the proton pump inhibitors (PPIs) that inhibits gastric acid secretion through an interaction with (H^+/K^+)-ATPase in gastric parietal cells [1]. This drug, which has an asymmetric sulfur in its chemical structure, is clinically administered as a racemic mixture of *R*(+)- and *S*(-)-enantiomers (Fig. 1). However, it was reported that the plasma concentrations of (*R*) - lansoprazole were consistently higher than those of the (*S*)-enantiomer in healthly subjects after oral administration of 30 mg of recemic lansoprazole [2]. It was considered that such a difference in the enantioselective pharmacokinetics of lansoprazole was likely due to its stereoselective protein binding and metabolism. *In vitro* experiments have demonstrated that the unbound fraction of (*S*) - lansoprazple was approximately 2-fold greater than that of the (*R*)-enantiomer when racemic lansoprazole was added to human serum [2], on the other hand, the intrinsic clearance (V_{max}/K_m), which is useful for the estimation of *in vivo* clearance rate [3], for the sulfoxidation of (*S*)-lansoprazole in human liver microsomes was 3.8-fold higher than that for (*R*)-enantiomer [4].

Lansoprazole is extensively metabolized in the human liver to 5-hydroxylansoprazole and lansoprazole sulfone, which are mainly catalyzed by CYP2C19 and CYP3A4, respectively [5]. Tacrolimus, an immunosuppressive agent, is also metabolized by CYP3A enzyme. Although



(*R*)-Lansoprazole



(*S*)-Lansoprazole

Fig. 1 Chemical structures of (*R*)- and (*S*)-lansoprazole

PPIs such as lansoprazole are generally coadministered with tacrolimus in renal transplant recipients suffering from gastric ulcer disease [6], the pharmacokinetics of lansoprazole in renal transplant patients receiving tacrolimus is not clarified enough until now. The purpose of this study is to evaluate the pharmacokinetics of lansoprazole enantiomers in renal transplant patients with CYP2C19 normal (extensive) metabolizer, who are subjected to simultaneous immunosuppressive therapy consisting of tacrolimus and mycophenolate mofetil.

Experimental

Reagents and chemicals

Lansoprazole enantiomers were purchased from Takeda Pharmaceutical (Osaka, Japan). (*S*)-Omeprazole used as the internal standard was kindly donated by the AstraZeneca (Mölndal, Sweden). The optical purity of (*S*)-omeprazole was 99.8 - 100% (data was provided by AstraZeneca). The Oasis HLB extraction cartridge was purchased from Waters (Milford, MA, USA). All solvents used were of HPLC grade (Wako Pure Chemical Industries, Osaka, Japan). All other reagents and chemicals were purchased from Wako Chemical Industries or Nacalai Tesque (Kyoto, Japan).

Patients

This study was approved by the Ethics Committee of Akita University Hospital, and all patients gave written, informed consent. The 30 mg of Takepron® brand of lansoprazole (Takeda) at 8 a.m. (30 min after the breakfast) was taken in renal transplant recipients receiving combination immunosuppressive therapy consisting of tacrolimus and mycophenolate mofetil, were given equally divided doses every 12 hours in designated time (9 a.m. and 9 p.m.). Meals were served at 7:30 a.m., 12:30 p.m., and 6 p.m. daily. Meal content (Japanese food) varied each day and for each patient, but energy, fat, protein, and water content was standardized (energy:1700-2400 kcal, protein:70-90g, fat:40- 50g, and water: 1600-2000mL) depending on body weight. On day 28 after renal transplantation, whole blood samples (2mL) were collected by vein puncture at 1, 2, 3, 4, 5, 7, 10, 13 and 24hr after oral lansoprazole administration. The plasma was separated by centrifugation at 1900×g for 15 min and stored at -30℃ until analysis, which was usually carried out within 1week. Patient plasma (100 μL) was extracted as described below and injected into the HPLC system.

CYP2C19 genotyping

Genotyping procedures identifying CYP2C19 wild - type gene and two mutated allele, CYP2C19*2 in exon 5 and CYP2C19*3 in exon 4, were performed by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method [7].

Analytical procedures

The plasma concentrations of lansoprazole enantiomers were measured by the reverse-phase HPLC method [8]. After (*S*)-omeprazole (20ng) in methanol (10 μL) was added to plasma samples (100 μL) as an internal standard, the plasma samples were diluted with water (1.0mL), and the solution was vortexed for 30 sec. This mixture was applied to an Oasis HLB extraction cartridge that had previously been activated with methanol (1.0mL) followed by water (1.0mL). The cartridge was washed with water (1.0mL) and 40% methanol in water (1.0mL) and then eluted with 80% methanol in water (1.0mL). The eluate was evaporated to

Table 1 Recipients Characteristics

Patients No	Renal Transplantation	Age	Sex	Smoking	Weight	Immunosuppressant (mg/day) Tacrolimus	MMF	CYP2C19 Genotype
1	HD	29	M	-	118	34	2000	*1/*1
2	HD	23	F	-	53	10	2000	*1/*1
3	HD	34	M	-	59	18	2000	*1/*1
4	HD	54	M	-	75	22	2000	*1/*1
5	HD	30	M	-	60	18	2000	*1/*3
6	HD	34	M	-	54	18	2000	*1/*2
7	HD	27	F	-	50	10	1500	*1/*1
8	HD	47	F	-	52	18	1500	*1/*2
9	HD	50	F	-	55	8	2000	*1/*2
10	HD	48	F	-	53	12	2000	*1/*1

HD: hemodialysis, MMF: mycophenolate mofetil

dryness in vacuum at 60℃ by a rotary evaporator (Iwaki, Tokyo, Japan). The residue was dissolved in methanol (50 μL) with vortex-mixing for 30 sec and then mobile phase (50 μL) with vortex-mixing for 30 sec. An aliquot solution (50 μL) was injected into the HPLC apparatus. The apparatus used for HPLC was a Model 510 chromatography pump (Waters) equipped with a Waters 486 ultraviolet detector. The wavelength was set at 285nm. Test samples were introduced using a Waters 712 WISP auto sampler with an effective volume (50 μL). The HPLC column used was a Chiral CD-Ph (250mm×4.6mm I.D., Shiseido, Tokyo, Japan). The mobile phase consisted of 0.5 *M* $NaClO_4$ - acetonitrile - methanol (6:3:1, v/v), which was degassed in an ultrasonic bath prior to use. A flow-rate of 0.5mL/min was used at ambient temperature. The lower limit of quantification of this assay for each enantiomer of lansoprazole was 10ng/mL. The coefficient of variation of inter- and intra-day assay was <5.9% and accuracy was within 4.9% for each analyte (concentration range 10-2000ng/mL). The linearity of this assay was set between 10 and 2000ng/mL (r^2>0.999 of the regression line) for each analyte.

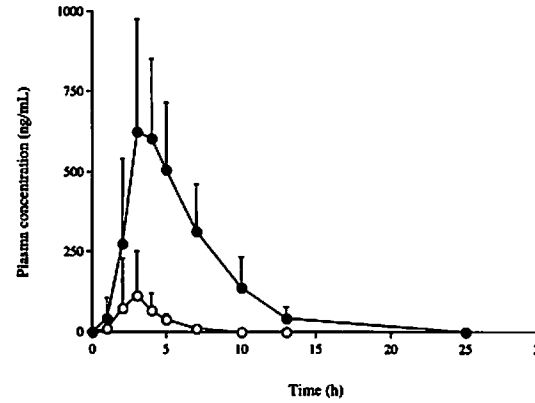


Fig. 2 Plasma concentration - time profiles of (*R*) - lansoprazole (*solid circles*) and (S)-lansoprazole (*open circles*) after 30mg oral dose of racemic lansoprazole to ten renal transplant recipients.

Statistical analysis

A pharmacokinetic analysis of lansoprazole enantiomers were carried out by a standard non-compartmental method using WinNonlin (Pharsight Co., CA, version 4.0.1). The total area under the observed plasma concentration-time curve (AUC) was calculated by using the linear trapezoidal rule. The maximum plasma level (C_{max}) and time to reach the peak (T_{max}) were obtained directly from the profile. All results were expressed as mean values ± SD. Statistical comparisons of the parameter were made by one - way analysis of variance,

Table 2 Pharmacokinetic Parameters of (*R*)-and (*S*)-Lansoprazole in Ten Renal Transplant Patients

Parameters	(*R*)-Lansoprazole	(*S*)-Lansoprazole	*R/S*
C_{max} (ng/mL)	784 ±207**	194 ±78	4.04 ±0.44
T_{max} (h)	3.6 ±1.1	2.8 ±1.3	1.3 ±0.4
MRT_{0-24} (h)	5.5 ±1.3	4 ±1.2	1.4 ±0.4
half-life (h)	1.83 ±0.94	1.28 ±0.39	1.43 ±1.0
AUC_{0-24} (ng·h/mL)	3837 ±1239**	478 ±175	8 ±4.0
CL/F (mL/hr/kg)	131 ±105**	894 ±527	0.15 ±0.03
Vd/F (mL/kg)	261 ±172**	1643 ±1055	0.16 ±0.10

**p<0.01 compared with (*S*)-lansoprazole

supplemented with multiple comparison procedure of Fisher in the StatView program, version 5.0 (SAS Institute, Cary, NC), and p values of less than 0.05 were considered to be statistically significant.

Results

The patient profile was shown in Table 1, and the mean plasma concentration-time curves of (*R*)- and (*S*)-lansoprazole in ten renal transplant patients after oral administration of racemic lansoprazole (30mg) are shown in Fig. 2. The pharmacokinetic parameters for their compounds are given in Table 2. The mean plasma concentrations of (*R*)-lansoprazole at all time points were significantly higher than those of (*S*)-enantiomer. The mean maximum concentration (C_{max}) for (*R*)-lansoprazole was 784±207ng/mL, and that of the (*S*)-enantiomer was 194± 78ng/mL, respectively (p<0.01). The time required to reach the maximum concentration (T_{max}) of (*R*)- and (*S*)- lansoprazole were around 3.6 and 2.8h, respectively. The half-life ($t_{1/2}$) values for (*R*)- and (*S*)-lansoprazole were 1.83 and 1.28h, respectively. Consequently, the mean AUC_{0-24} values for (*R*)-lansoprazole were about 8-fold greated compared with that for the (*S*)-enantiomer (3837 and 478ng · h/mL, respectively) (p<0.01). Furthermore, the CL/F and Vd/F values of (*S*)-lansoprazole were also significantly greater than those of (*R*)-enantiomer (p<0.01).

Discussion

After renal transplantation, immunotherapy has to continue throughout the graft's lifetime. In the present study, we studied the pharmacokinetics of lansoprazole enantiomers in ten renal transplant recipients with CYP2C19 extensive metabolizers receiving tacrolimus after transplantation, because CYP2C19 extensive metabolizers accounts for 74.6-84.8% of Japanese population [9-11]. It has been reported that the pharmacokinetic parameters of lansoprazole did not change after the repeated dosing compared with those after the single dosing [12, 13], because of very short half-life elimination of lansoprazole. Similarly to the previous results obtained from healthy subjects after a single dose [2], on day 28 after renal transplantation, the plasma concentrations of (*R*)-lansoprazole in recipients were also consistently higher than those of (*S*)-enantiomer. Further, the pharmacokinetic parameters of both enantiomers of lansoprazole in the present study were also in good agreement with previous reported values obtained from 12 healthy Korean subjects [2]. In vitro studies with

human liver microsomes or c-DNA expressed human CYP isoenzymes have shown that sulfoxidation of lansoprazole is catalyzed by CYP3A4 [4, 5]. Tacrolimus is also a substrate of CYP3A enzyme [14, 15]. Therefore, we can consider that the pharmacokinetic interaction in first-pass metabolism may have occurred between tacrolimus and lansoprazole [6]; however a significant change in the pharmacokinetics of lansoprazole was not observed in the present study. On the other hand, the T_{max} value of (*R*)-lansoprazole in renal transplant recipients (3.6h) was much longer than that in healthy subjects (2.0h), who not take any drugs and foods for 12h before the experiments [2]. This data suggest that the absorption of lansoprazole is greatly affected by meal ingestion, because of the enteric coated product of lansoprazole [16]. No effect of food on elimination half-life was observed, although it delayed the T_{max} value of lansoprazole. In conclusion, although the difference in the enantioselective pharmacokinetics of lansoprazole was reported likely due to its stereoselective protein binding and metabolism, the pharmacokinetic parameters of (*R*)- and (*S*)-lansoprazole in renal transplant recipients receiving tacrolimus as compared to typical healthy subjects were no signicant difference. In addition, the pharmacokinetic interaction between lansoprazole and tacrolimus was not observed in the present study.

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