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Effects of lansoprazole on pharmacokinetics and metabolism of theophylline

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Abstract The effect of the new substituted benzimidazole proton pump inhibitor, lansoprazole, on pharmacokinetics and metabolism of theophylline has been studied in healthy adults given oral lansoprazole 30 mg once daily for 11 days. On Days 4 and 11 of 300 mg aminophylline was simultaneously administered orally and blood samples for theophylline analysis were taken over 24 h. Urine samples were collected for up to 24 h and were assayed for theophylline and its major metabolites 1,3-dimethyluric acid (1,3-DMU), 1-methyluric acid (1-MU) and 3-methylxanthine (3-MX). The pharmacokinetic parameters of theophylline were determined, and the urinary recovery of unchanged theophylline and its major metabolites were calculated.

After administration of lansoprazole for 4 days, no significant alteration in the terminal elimination half-life ($t_{1/2\beta}$) or the mean residence time (MRT) was detected. However, there was a significant decrease of about 13% in the area under the plasma concentration-time curve (AUC) and a significant increase of about 19% in the apparent clearance (CL_{app}). Lansoprazole treatment for 11 days caused a significant decrease of approximately 12% in $t_{1/2\beta}$ and about 10% in the MRT of theophylline, although neither AUC nor CL_{app} showed a significant alteration. The excretion of 3-MX in the urine was significantly increased by about 20% after lansoprazole treatment for 4 and 11 days, although there was no significant alteration in the excretion of unchanged theophylline, 1,3-DMU or 1-MU.

The results indicate that repeated administration of lansoprazole to humans induces the hepatic microsomal P-450-dependent drug oxidation system that mediates *N*-1-demethylation of theophylline, consequently increasing its metabolism.

Key words Lansoprazole, Theophylline; proton pump inhibitor, theophylline metabolism, cytochrome P-450, drug interaction, enzyme induction, human

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The substituted benzimidazole proton pump inhibitors act by selectively inhibiting the proton pump or hydrogen-potassium ATPase on the secretory membrane of parietal cells, and are extensively used for the treatment of duodenal and gastric ulcers, reflux oesophagitis and the Zollinger-Ellison syndrome. It is generally accepted that substituted imidazoles, including benzimidazole compounds, inhibit hepatic microsomal cytochrome P-450-dependent drug oxidation enzymes [1, 2]. Therefore, many *in vitro* and *in vivo* studies have been carried out to elucidate the influence of the substituted benzimidazole proton pump inhibitors on the hepatic microsomal cytochrome P-450-dependent drug oxidation system. Omeprazole, a substituted benzimidazole proton pump inhibitor, has been shown to inhibit the hepatic microsomal cytochrome P-450 system, and to impair the metabolism of various coadministered drugs metabolised in the liver by this system [3].

Recently, clinical use of lansoprazole, a new substituted benzimidazole compound, has begun. An *in vitro* study showed that lansoprazole had the ability to inhibit the hepatic microsomal cytochrome P-450 system, and that this inhibitory activity was greater than that of omeprazole [4]. However, very little information about the effect of lansoprazole on the metabolism of coadministered drugs in humans has been published.

Theophylline (1,3-dimethylxanthine) is frequently used in the treatment of bronchial asthma and has a relatively narrow therapeutic plasma concentration range. Approximately 90% of administered theophylline is metabolised by the hepatic cytochrome

P-450 system and only about 10% is excreted unchanged in the urine. Therefore, the elimination of theophylline can be influenced by many factors that affect the hepatic cytochrome P-450 system, and various drugs, such as cimetidine, diltiazem, α-interferon *etc.* have been shown to affect metabolism of theophylline in the liver [5, 6]. Theophylline can be used as a marker drug, like antipyrine, to evaluate the effect on hepatic cytochrome P-450-dependent oxidative drug metabolism [7]. It is possible that theophylline and lansoprazole may be used simultaneously in clinical treatment, and that lansoprazole, which contains a benzimidazole moiety, may affect the metabolism of theophylline. Nevertheless, little information is available concerning any interaction between theophylline and lansoprazole.

In the present study, in order to investigate the effect of lansoprazole on the theophylline metabolism in humans, we determined the pharmacokinetic parameters of theophylline and the urinary excretion of its metabolites in healthy adult volunteers treated with lansoprazole.

Subjects and methods

Chemicals and reagents

Takepron® capsules, each containing 30 mg lansoprazole, were purchased from Takeda Pharmaceutical Co., Ltd., Osaka, Japan. Aminophylline powder containing theophylline was obtained from Maruishi Pharmaceutical Co., Ltd., Osaka, Japan. Methanol (HPLC grade) was obtained from Nacalai Tesque, Kyoto, Japan. Theophylline, 7-(2-hydroxyethyl)-theophylline as an internal standard (I.S.), 3-methylxanthine (3-MX), 1,3-dimethyluric acid (1,3-DMU), 1-methyluric acid (1-MU) and *tetra-n*-butylammonium hydrogen sulphate (TBA) were purchased from Sigma (St. Louis, MO, U.S.A.). All other chemicals were of reagent grade.

Clinical procedure

Subjects with febrile illnesses within 14 days prior to the start of the study ordering the trial were excluded. Seven subjects completed the trial. They were healthy non-smoking male volunteers, aged 22 to 38 *mean* 30.3 (5.9) y, weighing 54 to 90 kg *mean* 69.4 (12.6) kg (Table 1).

Subjects were judged to be healthy by a physician based on pretreatment medical history and normal physical examination. No medication was allowed for 7 days prior to or during the study.

The study was an open, comparative non-randomised, within subject, 2-week trial. The study protocol was reviewed and approved by the Health Authority Ethics Committee in Kyoto Prefectural University of Medicine, and was explained in detail to the subjects, each of whom gave their informed consent to participation.

The subjects received by mouth 300 mg aminophylline (containing 240 mg theophylline), on an empty stomach, at 9:00 a.m. on Days 4 and 11. On Days 1–11, 30 mg lansoprazole was administered orally at 9:00 h.

Blood samples (3 ml) were collected on Days 4–5 and 11–12 at 0.5, 1, 2, 4, 6, 9, 12 and 24 h after theophylline administration. Plasma was obtained by centrifugation at $1,500 \times g$. On the same days, urine samples were also collected from 0 to 2, 2–4, 4–6, 6–8, 8–12 and 12–24 h. The plasma and urine samples were stored at −20 °C until analysed.

From 2 to 8 weeks before the trial, each subject received orally 300 mg aminophylline. As a control, plasma and urine samples over 24 h were obtained by the same method as on Days 4–5 in the trial.

The subjects maintained a standardised diet throughout the trial and they excluded beverages containing methylxanthine for 72 h before and on all of the sampling days. The subjects did not take any other drugs and were not allowed to drink alcoholic beverages during the study.

Bioanalytical methods

Theophylline in plasma

Plasma theophylline concentrations were determined by a fluorescence polarization immunoassay technique using an Abbott TDX™–Theophylline system kit (Abbott Laboratories, Chicago, IL).

Table 1 Details of the subject and pharmacokinetic parameters derived from the plasma theophylline concentration data obtained after the oral administration of aminophylline alone (Cont) and during coadministration of lansoprazole on Days 4–5 (Lan4) and Days 11–12 (Lan11)

Subject		A	B	C	D	E	F	G	Mean	(SD)
Age (years)		38	30	33	25	26	38	22	30.3	(5.9)
Weight (kg)		85	61	65	59	72	54	90	69.4	(12.6)
Theophylline dose ($mg \cdot kg^{-1}$)		2.82	3.93	3.69	4.07	3.33	4.44	2.67	3.57	(0.61)
$t_{1/2\beta}$ (h)	Cont	8.56	10.76	8.52	6.54	6.83	6.90	7.95	8.01	(1.36)
	Lan4	9.50	7.52	7.32	5.62	6.23	6.50	5.75	6.92	(1.24)
	Lan11	8.20	8.84	7.73	5.60	6.08	6.08	6.93	7.07	(1.13)**
AUC	Cont	81.8	121.1	98.4	84.0	87.6	97.1	75.6	92.2	(14.0)
($\mu g \cdot h \cdot ml^{-1}$)	Lan4	90.3	104.1	93.4	70.4	73.9	82.3	46.7	80.2	(17.4)*
	Lan11	87.6	120.7	94.3	76.5	75.7	94.1	61.3	87.2	(17.5)
MRT(h)	Cont	12.5	14.8	12.1	9.5	9.9	9.8	11.4	11.4	(1.8)
	Lan4	14.2	11.0	10.6	8.2	9.0	9.5	8.5	10.1	(1.9)
	Lan11	12.2	12.4	10.9	8.3	9.0	8.8	10.1	10.3	(1.5)**
$CL_{app}(l \cdot h^{-1} \cdot kg^{-1})$	Cont	0.035	0.033	0.038	0.048	0.038	0.046	0.035	0.039	(0.006)
	Lan4	0.031	0.038	0.040	0.058	0.045	0.054	0.057	0.046	(0.010)*
	Lan11	0.032	0.033	0.039	0.053	0.044	0.047	0.044	0.042	(0.007)

*,** Significant difference between lansoprazole treatment (Lan4, Lan11) and control (Cont)
* $P < 0.05$; ** $P < 0.005$

Theophylline and metabolites in urine

A selective and sensitive HPLC method was used for the simultaneous determination of theophylline and its major metabolites by a modification of a previously reported method [8]. Urine/ml was centrifuged for 20 min at 3,000 r.p.m. after the addition of 0.1 M carbonate buffer, pH 11.0 (0.5 ml). The supernatant fraction 150 µl was saturated with 400 mg ammonium sulphate, and, after addition of 1 mM 7-(2-hydroxyethyl)-theophylline 50 µl as the internal standard and 0.1 M TBA 100 µl, was mixed in a vortex mixer for 30 s. The mixture was extracted with 2 ml portions of ethylacetate - chloroform - isopropanol (45:45:10, v/v). 1 ml of organic phase was evaporated to dryness under nitrogen gas and reconstituted in 200 µl mobile phase. The reconstituted sample (25 µl) was injected onto the chromatography column. The system consisted of an LC-6A liquid delivery module (Shimadzu), SPD-6A UV-detector, and a reversed-phase column (Cosmosil 5C-18, 4.6 × 150 mm i.d.). The mobile phase was a mixture of methanol (HPLC grade) and 0.01 M sodium acetate buffer (pH4.9) containing 5 mM TBA (11:89, v/v), at a flow-rate of 1.0 ml · min^{-1}, and the oven temperature was 35° C. The column eluate was monitored at 275 nm, and the area under each peak was calibrated with a Shimadzu CR-3A Chromatopac. Theophylline, 1,3-DMU, 1-MU and 3-MX were eluted at retention times of 10.5 min, 7.4 min, 5.8 min and 3.7 min, respectively.

Data analysis

The terminal elimination rate constant (β) of the theophylline concentration-time curves after oral dosing was determined by linear regression of at least five data points in the terminal portion of the plasma concentration-time plots. The area under the plasma concentration-time curve after oral administration (AUC) was calculated by the trapezoidal rule with the addition of the correction term from the last measured point to infinity, namely $C_{p(last)}/\beta$. The area under the first moment curve to the last measured plasma concentration after oral administration (AUMC) was calculated by trapezoidal rule with the addition of a correction term from the last measured point to infinity, viz $t_{(last)} \cdot C_{p(last)}/\beta + C_{p(last)}/\beta^2$. The mean residence time (MRT) was determined by dividing AUMC by AUC. The terminal elimination half-life ($t_{1/2\beta}$) was determined as ln2/β. The apparent plasma clearance (CL_{app}) was determined by dividing the oral dose by the AUC (Table 1).

The urinary excretion (% of dose) of unchanged theophylline and its metabolites was calculated by dividing the quantity excretion by the administered dose (Table 2). The cumulative excretion of theophylline (unchanged theophylline and its major metabolites) for an infinite time (Ae) was determined from the measured excretion with the addition of the excretion after the last measured point to the infinity calculated by extrapolation from the excretion rate-time plot. The total recovery of theophylline was calculated by dividing Ae by the administered dose. The renal clearance (CLR) was determined by dividing Ae by AUC (Table 3).

Table 2 Urinary excretion (% of dose) of unchanged theophylline and its metabolites (1,3-dimethyluric acid: 1,3-DMU, 1-methyluric acid: 1-MU and 3-methylxanthine: 3-MX) over 24 h after oral administration of aminophylline (Cont) and on Days 4–5 (Lan4) and Days 11–12 (Lan11) of lansoprazole treatment

(% dose)	Cont Mean (SD)	Lan4 Mean (SD)	Lan11 Mean (SD)
Theophylline	8.4 (2.4)	8.3 (1.6)	8.4 (1.8)
1,3-DMU	19.5 (2.8)	20.4 (3.4)	19.4 (3.4)
1-MU	19.7 (2.7)	22.2 (5.7)	25.5 (10.7)
3-MX	4.9 (1.3)	6.0 (1.3)*	6.1 (1.6)*
Total	52.6 (6.2)	56.9 (5.5)	59.4 (11.6)

* Significant difference between control (Cont) and lansoprazole treatment (Lan4, Lan11) ; $P < 0.05$

Table 3 Urinary excretion of total theophylline. (Ae, Cumulative excretion to infinity obtained by extrapolating from the excretion rate-time plot; Ae%, total recovery extrapolated to infinity; CLR renal clearance)

	Cont Mean (SD)	Lan4 Mean (SD)	Lan11 Mean (SD)
Ae (mg)	147 (16.8)	155 (16.4)*	168 (41.4)
Ae% (% dose)	61.2 (7.0)	64.4 (6.8)*	69.9 (17.2)
CLR (l/h)	1.62 (0.28)	2.07 (0.68)*	2.07 (0.86)

* Significant difference between control (Cont) and lansoprazole treatment (Lan4, Lan11); $P < 0.05$

The parameters were determined for each individual. The Values are expressed as *mean* with (SD). Differences were examined statistically by two-way ANOVA.

Results

Individual pharmacokinetic parameters for the 7 subjects from whom complete the concentration-time profiles were obtained are shown in Table 1.

On Days 4–5 of the trial (Lan 4), after daily lansoprazole for 4 days, the mean values of $t_{1/2\beta}$ (6.92 (1.24) h) and MRT (10.1 (1.9, h) were slightly decreased by approximately 13% and 11%, respectively, compared to the corresponding control values (8.01 (1.36) h and 11.4 (1.8) h, respectively); the decreases were not statistically significant. However, on Days 4–5 there was a significant decrease of about 13% in the mean AUC (80.2 (17.4) µg · h · ml^{-1}) ($P < 0.05$) from that in the control period (92.2 (14.0 µg · h · ml^{-1}), and there was also a significant increase of about 19% in the mean value of CL_{app} (0.046 (0.010) l · h^{-1} · kg^{-1}) ($P < 0.05$) from the control value (0.039 · (0.006) l · h^{-1} · kg^{-1}).

Lansoprazole treatment for 11 days (Lan 11) led to significant decreases in the mean $t_{1/2\beta}$ (7.07 (1.13) h) and MRT (10.3 (1.5) h) of approximately 12% and 10%, respectively ($P < 0.005$). On Days 11–12, the mean AUC (87.2 (17.5) µg · h · ml^{-1}) showed was about 6% lower, and the mean value of CL_{app} (0.042 (0.007) l · h^{-1} · kg^{-1}) showed a small increase of about 7%; these difference were not significant.

The mean urinary excretion (% dose) of unchanged theophylline and its major metabolites were listed in Table 2. After lansoprazole treatment both for 4 and 11 days, there was no statistically significant alteration in the excretion of unchanged theophylline or 1,3-dimethyluric acid (1,3-DMU). The excretion of 1-methyluric acid (1-MU) was increased by approximately 18% (Lan 4) and 29% (Lan 11), but neither change was significant. The excretion of 3-methylxanthine (3-MX) increased significantly by about 20% after lansoprazole treatment both for 4 and 11 days ($P < 0.05$). It is generally accepted that 1-methylxanthine (1-MX) , a theophylline metabolites, is immediately transformed in the liver into 1-MU. Therefore, in

the present study 1-MX could not be detected. The mean cumulative excretion of theophylline for an infinite time (Ae), the urinary recovery of theophylline to infinity (Ae%), and the renal clearance (CLR) are listed in Table 3. On Days 4–5 Ae% and CLR showed significant increases of 5.2% and 27.6%, respectively ($P < 0.05$). On Days 11–12 Ae% and CLR were increased by 14.2% and 27.7%, respectively, but the differences were not significant.

Discussion

Lansoprazole is a benzimidazole sulphoxide, a representative of new class of proton pump inhibiting compounds, which is available as a gastric acid antisecretory drug. It has been reported that lansoprazole is metabolised by *O*-dealkylation by the hepatic cytochrome P-450-dependent drug oxidation enzyme system, by oxidation and reduction of the sulphinyl group, and hydroxylation of the benzimidazole-ring and the methyl group [9]. Studies *in vitro* with human liver microsomes and hepatocytes have indicated that both cytochrome (CYP) P-450 3A4 and 2Cmeph, specific isoenzymes of the cytochrome (CYP) P-450 subfamily, mediate 5-hydroxylation of the benzimidazole, and CYP3A4 is the major isoenzyme involved in sulphone and sulphide formations [10]. Recently, Simon et al. demonstrated that lansoprazole showed noncompetitive mixed-type inhibition of lonazolac hydroxylase and 7-ethoxycoumarin dealkylase, respectively [4]. Miwa et al. reported that the repeated administrations of lansoprazole for 5 days to the rat increased the protein content of hepatic microsomes and induced cytochrome P450-dependent drug oxidative enzymes in the liver [11].

In the present study, we have reported for the first time the effect of lansoprazole on the metabolism of theophylline, including the urinary excretion of its three major metabolites in man. Our results show that repeated administration of lansoprazole significantly increased AUC and CL_{app} ($P < 0.05$) and decreased $t_{1/2\beta}$ and MRT ($P < 0.005$) and that it also significantly increased the urinary excretion of 3-MX ($P < 0.05$). Lansoprazole did not alter the absorption of theophylline, as on Days 4–5 the urinary recovery over an infinite time showed a significant increase, while a significant decrease was observed in AUC and a significant increase in CL_{app}. Granneman et al. described how treatment with 60 mg lansoprazole once a day for 7 days caused the slight but significant decrease of about 14% in the AUC of theophylline [12]. In the present study, a decrease of about 13% in AUC was observed after the treatment with 30 mg lansoprazole once a day over 4 days. Our findings suggest that repeated administration of lansoprazole in the therapeutic dose used in Japan causes a decrease similir to that found by Granneman et al.

Theophylline (1,3-dimethylxanthine) is extensively metabolised by the hepatic microsomal cytochrome P-450-dependent drug oxidation system. Approximately 30–40% is excreted as the oxidation product 1,3-dimethyluric acid (1,3-DMU), about 20–30% is metabolised by *N*-3-demethylation to 1-methylxanthine (1-MX), which is immediately transformed into 1-methyluric acid (1-MU) by xanthine oxidase, and about 15–20% is metabolised by *N*-1-demethylation to 3-methylxanthine (3-MX) [13, 14]. In the present study, we the urinary recovery of 3-MX showed a significant 20% increase after treatment with lansoprazole both for 4 and 11 days ($P < 0.05$). These and the present findings suggested that repeated coadministration of lansoprazole for at least 4 days induces the hepatic microsomal CYP1A2 that mediates *N*-1-demethylation of theophylline especially, and increases the metabolism of theophylline. The clinical importance of the interaction between lansoprazole and theophylline remains to be evaluated.

Nousbaum et al. reported that omeprazole, a substituted benzimidazole proton pump inhibitor, is an inducer of CYP1A2 [15]. However, Guglar and Jensen reported that no significant change occurred in the disposition of theophylline after omeprazole treatment [16]. On the other hand, many clinical studies have demonstrated that omeprazole impairs the elimination of various coadministered drugs, such as diazepam, phenytoin and warfarin [17]. These findings pointed to the possibility that lansoprazole would be an inducer of CYP1A2 and a competitive inhibitor of CYP3A4 and CYP2Cmeph, and also to the prediction that lansoprazole treatment would increase the clearance of theophylline administered simultaneously. A recent *in vitro* study revealed that the inhibitory activity of lansoprazole on the hepatic microsomal cytochrome P-450 isozymes was much greater than that of omeprazole [4], and the present results show that repeated administration of lansoprazole to humans causes induction of the hepatic microsomal cytochrome P-450-dependent drug oxidation system, especially CYP1A2. Further studies are necessary to elucidate the interactions between lansoprazole and coadministered drugs.

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