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Effects of Epigallocatechin gallate on the Pharmacokinetics of Nicardipine after Oral and Intravenous Administration of Nicardipine in Rats

조선대학교 대학원

약학과

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흰쥐에서 에피가로카테친이 경구 및 정맥으로 투여된 니칼디핀의
약물동태에 미친 영향

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이 논문을 약학석사학위신청 논문으로 제출함.

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Effects of epigallocatechin gallate on the pharmacokinetics of nica rdipine after oral and intravenous administration of nicardipine in rats

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Epigallocatechin gallate (EGCG), a natural polyphenol compound found in fruits and red wine, has irreversible inhibition for cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) *in vitro*. This study was to investigate the effect of EGCG on the pharmacokinetics of nicardipine after orally or intravenously administered nicardipine in rats. Nicardipine was administered orally (12 mg/kg) or intravenously (i.v., 4 mg/kg) without or with oral administration of EGCG (0.6, 3 or 12 mg/kg) to rats. Compared with the control group (given nicardipine alone), the area under the plasma concentration–time curve (AUC) was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) increased by 56.2–78.7%, and the peak concentration (C_{max}) was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) increased by 30.1–47.5% in the presence of EGCG after orally administration of

nicardipine. EGCG significantly ($P < 0.05$, 3 or 12 mg/kg) decreased the total body clearance (CL/F) of nicardipine by 35.9–44.0%. Consequently, the relative bioavailability (R.B.) of nicardipine was increased by 1.19- to 1.79-fold, the absolute bioavailability (A.B.) of nicardipine in the presence of EGCG was 17.2–19.7%, which was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) enhanced compared with that of the control group (11.0%). Compared to the i.v. control, EGCG did not significantly change pharmacokinetic parameters of i.v. administration nicardipine.

The enhanced oral bioavailability of nicardipine suggested that intestinal-mediated CYP3A4 metabolism and P-gp-mediated efflux of nicardipine are inhibited by EGCG. Based on these results, nicardipine dosage should be adjusted when given with EGCG or EGCG-containing dietary supplement.

Key words: Nicardipine; EGCG; CYP3A4; P-gp; Pharmacokinetics; Rats

국 문 초 록

흰쥐에서 에피가로카테친이 경구 및 정맥으로 투여된 니칼디핀의 약물동태에 미친 영향

임 태 환
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고혈압 환자에서 항산화제인 에피가로카테친과 고혈압치료제인 니칼디핀과 병용처방이 가능하다. 시험관실험에서 에피가로카테친은 사이토크롬 P450 3A4 (CYP3A4)와 P-당단백질 (P-gp)를 억제한다고 보고되었다. 그러므로 에피가로카테친이 CYP3A4 와 P-gp 의 기질인 니칼디핀의 약물동태에 미칠 것으로 사료되며 흰쥐에 에피가로카테친 (0.6, 3, 12 mg/kg)을 니칼디핀과 경구 (12 mg/kg) 및 정맥 (4 mg/kg)으로 병용투여하여 본 연구를 실시하였다. 대조군에 비해 혈장농도곡선하면적 (AUC) 및 최고혈중농도 (C_{max}) 는 대조군에비해 에피가로카테친 병용투여군에서 유의성 (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) 있게 증가하였다. 대조군에 비해 토달클리어런스 (CL/F)는 병용투여시 유의성($P < 0.05$, 3 및 12 mg/kg) 있게 감소하였다. 대조군에

비해 절대적생체이용률은 유의성 (3 mg/kg, P < 0.05; 12 mg/kg, P < 0.01) 있게 증가되었으며 상대적생체이용률은 1.19-1.79 배로 증가되었다. 이것은 에피가로카테친이 소장 또는 간장에서 CYP3A4 와 P-당단백질을 억제시켜 니칼디핀의 생체이용률을 증가시킨 것으로 사료된다.

임상에서 에피가로카테친과 니칼디핀을 병용투여시 니칼디핀의 용량를 조절하는 것이 바람직하다고 사료된다.

Introduction

Nicardipine, a dihydropyridine calcium channel antagonist, causes coronary and peripheral vasodilatation by blocking the influx of extracellular calcium across cell membranes. Nicardipine is arterioselective and effective for the treatment of hypertension, myocardial ischemia, and vasospasm in surgical patients (Kishi *et al.,* 1984; Hysing *et al.,* 1986). Nicardipine has also been used experimentally as a probe to study the effects of calcium channel antagonists on the role of sympathetic nervous system activity in the development of cardiovascular risk (Van Swieten *et al.,* 1997). The pharmacokinetics of nicardipine are non-linear due to hepatic first-pass metabolism, and show a bioavailability of about 35% following a 30 mg dose at steady state (Graham *et al.,* 1984, 1985). They are primarily substrates of CYP3A subfamily enzymes, especially CYP3A4 in humans, and metabolized to pharmacologically inactive forms (Higuchi & Shiobara, 1980; Guengerich *et al.,* 1986; Guengerich, 1991). In addition, nicardipine is also a P-glycoprotein (P-gp) substrate (Hu *et al.,* 1996; Wang *et al.,* 2000).

Flavonoids represent a group of phytochemicals that are produced by various plants in high quantities (Dixon and Steele, 1999). They exhibit a wide range of beneficial biological activities including antioxidative, radical scavenging, antiatherosclerotic, antitumor and antiviral effects (Nijveldt *et al.,* 2001). EGCG is the major flavanoid found in green tea and is also known as catechins (Chu and Juneja, 1997). EGCG has a wide range of biological and pharmacological activities,

including antioxidant (Higdon and Frei, 2003), antiatherosclerotic and anticarcinogenic activities (Kuroda and Hara, 1999; Nijveldt *et al.,* 2001). EGCG inhibited human CYP3A4 with the IC_{50} value of 10 μM (Muto *et al.,* 2001), and has an inhibitory effect on P-gp in human Caco-2 cells (Jodoin *et al.,* 2002), but does not down-regulate MDR1 gene transcription and P-gp expression (Qian *et al.,* 2005). Hong et al. (2003) reported that EGCG and its methyl metabolites are substrates for MRP1 and MRP2. EGCG is also subject to the UDP-glucuronosyltransferase, sulfotransferase and catechol-O-methyltransferase mediated phase II biotransformation (Lu *et al.,* 2003). EGCG inhibited the efflux of P-gp substrates, diltiazem and quercetin in KB-C2 cell (Kitagawa *et al.,* 2004).

As a dual inhibitor of CYP3A4 and P-gp, EGCG might affect the bioavailability and pharmacokinetics of nicardipine when EGCG and nicardipine were used concomitantly for the prevention or therapy of cardiovascular diseases as a combination therapy. However, the effect of EGCG on the pharmacokinetics of nicardipine has not been reported in vivo. This study focused on the investigation of the effect of EGCG on the pharmacokinetics of nicardipine in rats.

The low bioavailability of oral nicardipine is mainly due to pre-systemic metabolism and P-gp mediated efflux in the intestine. EGCG, a dual inhibitor of CYP3A4 and P-gp, might improve the pharmacokinetics of nicardipine in combination therapy, although adverse effects may occur if doses are not adequate. Therefore, the aim of this study was to investigate the pharmacokinetics of

nicardipine in the presence of EGCG in rats.

Materials and Methods

Chemicals and apparatus

Nicardipine, EGCG and nimodipine [an internal standard for high-performance liquid chromatograph (HPLC) analysis for nicardipine] were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). HPLC grade acetonitrile were acquired from Merck Co. (Darmstadt, Germany). Other chemicals for this study were of reagent grade.

Apparatus used in this study were a HPLC equipped with a Waters 1515 isocratic HPLC Pump, a Waters 717 plus autosampler and a Waters™ 474 scanning fluorescence detector (Waters Co., Milford, MA, USA), a HPLC column temperature controller (Phenomenex Inc., CA, USA), a Bransonic® Ultrasonic Cleaner (Branson Ultrasonic Co., Danbury, CT, USA), a vortex-mixer (Scientific Industries Co., NY, USA) and a high-speed micro centrifuge (Hitachi Co., Tokyo, Japan).

Animal experiments

Male Sprague–Dawley rats of 7–8 weeks of age (weighing 270–300 g) were purchased from Dae Han Laboratory Animal Research Co. (Choongbuk, Republic of Korea) and given free access to a commercial rat chow diet (No. 322-7-1; Superfeed Co., Gangwon, Republic of Korea) and tap water *ad libitum*. The animals were housed (two rats per cage) in a clean room maintained at a

temperature of 22 ± 2°C and relative humidity of 50–60%, with 12 h light and dark cycles. The rats were acclimated under these conditions for at least 1 week. All animal studies were performed in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA) and the Animal Care Committee of Chosun University (Gwangju, Republic of Korea) approved the protocol of this animal study. The rats were fasted for at least 24 h prior to beginning the experiments and had free access to tap water. Each animal was anaesthetized lightly with ether. The left femoral artery and vein were cannulated using polyethylene tubing (SP45, I.D. 0.58 mm, O.D. 0.96 mm; Natsume Seisakusho Co. LTD., Tokyo, Japan) for blood sampling and i.v. injection, respectively.

Oral and intravenous administration of nicardipine

The rats were divided into four groups (n = 6, each); an oral group (12 mg/kg of nicardipine dissolved in water; homogenized at 36 ^{o}C for 30 min; 3.0 mL/kg) without (control) or with 0.6, 3 or 12 mg/kg of oral EGCG, and an i.v. group (4 mg/kg of nicardipine, dissolved in 0.9% NaCl solution; homogenized at 36 ^{o}C for 30 min; 1.5 mL /kg) without (control) or with 0.6, 3 or 12 mg/kg of oral EGCG. Oral nicardipine was using a feeding tube, and EGCG was orally administered 30 min prior to oral or intravenous administration of nicardipine. Nicardipine for i.v. administration was injected through the femoral vein within 0.5 min. A 0.45 mL aliquot blood sample was collected into heparinized tubes from the femoral artery

at 0 (to serve as a control), 0.017 (at the end of infusion), 0.1, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h after intravenous infusion, and 0.1, 0.25, 0.5, 1, 2, 3, 6, 8, 12 and 24 h for oral study. The blood samples were centrifuged (13,000 rpm, 5 min), and the plasma samples were stored at –40˚C until HPLC analysis of nicardipine. Approximately 1 mL of whole blood collected from untreated rats was infused via the femoral artery at 0.25, 1, 3 and 8 h to replace the blood loss due to blood sampling.

HPLC assay

The plasma concentrations of nicardipine were determined by a HPLC assay method reported by Eastwood *et al.* (1990). Briefly, a 50 μL aliquot of nimodipine (2 μg/mL), a 20 μL aliquot of 2 N sodium hydroxide solution and 1.2 mL of tert-butylmethylether:Hexane (75:25) were added to a 0.2 mL aliquot of the plasma sample. The mixture was then stirred for 2 min and centrifuged (13,000 rpm, 10 min). A 1.0 mL aliquot of the organic layer was transferred to a clean test tube and evaporated at 35°C under a stream of nitrogen. The residue was dissolved in 200 μL of the mobile phase and centrifuged (13,000 rpm, 5 min). A 50 μL aliquot of the supernatant was injected into the HPLC system. Chromatographic separations were achieved using a Symmetry® C_{18} column (4.6 × 150 mm, 5 μm, Waters Co.), and a μBondapak™ C_{18} HPLC Precolumn (10 μm, Waters Co.). The mobile phase was acetonitrile:0.015 M KH_2PO_4 (60:40, v/v, pH 4.5) with 2.8 mM triethylamine,

which was run at a flow rate of 1.5 mL/min. Chromatography was performed at a temperature of 30˚C that was set by a HPLC column temperature controller. The UV detector was set to 254 nm. The retention times of nicardipine and the internal standard were 7.8 and 4.2 min, respectively (Figure 1). The detection limit of nicardipine in rat's plasma was 5 ng/mL. The coefficients of variation for nicardipine were below 14.1% (Figure 2).

Pharmacokinetic analysis

The plasma concentration data were analyzed by noncompartmental method using WinNonlin software version 4.1 (Pharsight Co., Mountain View, CA, USA). The elimination rate constant (K_{el}) was calculated by log-linear regression of nicardipine concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$. The peak concentration (C_{max}) and the time to reach peak concentration (T_{max}) of nicardipine in plasma were obtained by visual inspection of the data from the concentration–time curve. The area under the plasma concentration–time curve (AUC_{0-t}) from time zero to the time of last measured concentration (C_{last}) was calculated by the linear trapezoidal rule. The AUC zero to infinite ($AUC_{0-\infty}$) was obtained by the addition of AUC_{0-t} and the extrapolated area determined by C_{last}/K_{el}. Total body clearance (CL/F) was calculated by Dose/AUC. The absolute bioavailability (A.B.%) of nicardipine was calculated by $AUC_{oral}/AUC_{iv} \times Dose_{i.v.}/Dose_{oral} \times 100$, and the relative bioavailability (R.B.%) of nicardipine was estimated by $AUC_{with\ EGCG}/AUC_{control} \times$

100.

Statistical analysis

All mean values are presented with their standard deviation (Mean ± S.D.). Statistical analysis was conducted using a one-way ANOVA followed by *a posteriori* testing with Dunnett's correction. Differences were considered significant at a level of $p < 0.05$

Results

The mean plasma concentration–time profiles of oral nicardipine in the presence or absence of EGCG are illustrated in Figure 3. The mean pharmacokinetic parameters of nicardipine were also summarized in Table 3.

Figure 3 showed the plasma concentration–time profiles of nicardipine after oral administration at a dose of 12 mg/kg of nicardipine in rats with or without EGCG (0.6, 3 or 12 mg/kg), and the pharmacokinetic parameters of oral nicardipine are summarized in Table 3. The area under the plasma concentration–time curve (AUC) was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) increased by 56.2– 78.7%, and the peak concentration (C_{max}) was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) increased by 30.1–47.5% in the presence of EGCG after oral administration of nicardipine. EGCG significantly ($P < 0.05$, 3 or 12 mg/kg) decreased the total body clearance (CL/F) of nicardipine by 35.9–44.0%. Consequently, the relative bioavailability (R.B.) of nicardipine was increased by 1.19- to 1.79-fold, the absolute bioavailability (A.B.) of nicardipine in the presence of EGCG was 17.2–19.7%, which was significantly (3 mg/kg, $P < 0.05$; 12 mg/kg, $P < 0.01$) enhanced compared with that of the control group (11.0%). However, there was no significant change in the time to reach peak concentration (T_{max}) and the half-life ($t_{1/2}$) of nicardipine in the presence of EGCG.

The mean plasma concentration–time profiles of i.v. nicardipine in the presence

or absence of EGCG are illustrated in Figure 4. The mean pharmacokinetic parameters of nicardipine were also summarized in Table 4. Figure 4 showed the plasma concentration–time profiles of nicardipine after i.v. (4 mg/kg) without or with of EGCG (0.6, 3 or 12 mg/kg) to rats. As shown in Table 4, EGCG did not significantly change pharmacokinetic parameters of i.v. administration of nicardipine, suggesting that EGCG may improve the oral bioavailability of nicardipine by increasing the absorption or reducing gut wall metabolism.

Discussion

CYPs enzymes make a contribution significantly to the “first-pass” metabolism and oral bioavailability of many drugs. The “first-pass” metabolism of compounds in the intestine limits absorption of toxic xenobiotics and may ameliorate side effects. Moreover, induction or inhibition of intestinal CYPs may be responsible for significant drug and drug interactions when one agent decreases or increases the bioavailability and absorption rat constant of a concurrently administered drug (Kaminsky and Fasco, 1991).

Based on the broad overlap in the substrate specificities as well as co-localization in the small intestine, the primary site of absorption for orally administered drugs, CYP3A4 and P-gp have been recognized as a concerted barrier to the drug absorption (Cummins *et al.,* 2002; Benet *et al.,* 2003). Therefore, dual inhibitors against both CYP3A4 and P-gp should have a great impact on the bioavailability of many drugs where CYP3A4 metabolism as well as P-gp mediated efflux is the major barrier to the systemic availability. Besides the extensive metabolism by CYP3A4, nicardipine appeared to be the substrate of P-gp, suggesting that P-gp and CYP3A4 should act synergistically to limit the oral bioavailability of nicardipine (Saeki *et al.,* 1993; Wacher *et al.,* 2001).

Studies on drug interactions with grapefruit juice have provided much understanding of the role of intestinal CYP450 in the absorption of orally

administered drugs. CYP3A4 is the predominant P450 present in the small intestine (Kolars *et al*., 1992) Oral administered nicardipine is a substrate for CYP3A-mediated metabolism and P-gp-mediated efflux. The enhanced oral bioavailability of nicardipine might be due to decreased P-gp efflux and CYP3A metabolism of nicardipine in the intestine and/or liver. 0.6 mg/kg of EGCG did not significantly change pharmacokinetic parameters of nicardipine, possibly it can either inhibit or stimulate rat CYPs depending upon their structures, concentrations, and experimental conditions. This result appeared to be consistent with a previous report that a single oral administration of EGCG significantly increased enhanced the oral bioavailability of nicardipine in rats (Piao and Choi, 2008).

The increased bioavailability of orally administered nicardipine might be due to competitive inhibition of CYPs and P-gp in the intestine by EGCG, since the inhibition of CYP isoenzyme and P-gp in the liver and kidney was not marked after intravenous administration as mentioned above. These results suggest enhanced bioavailability of nicardipine must be mainly inhibited P-gp efflux and CYP3A metabolism in the intestine by EGCG.

Conclusion

While there was no significant effect on the i.v. pharmacokinetics of nicardipine, EGCG (3 or 12 mg/kg) significantly enhanced the oral bioavailability of nicardipine. Therefore, concomitant use of EGCG or EGCG-containing dietary supplements with nicardipine will require close monitoring for potential drug interactions.

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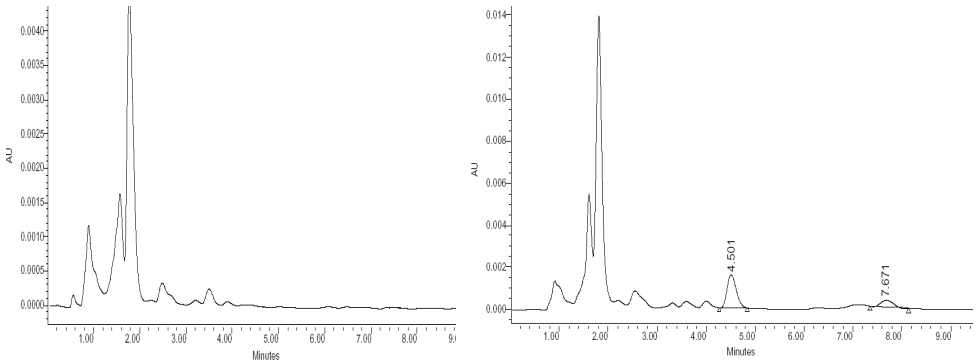

Figure 1. Chromatograms of the rat's blank plasma (A) and plasma spiked (B) with internal standard (IS, 4.5 min) and nicardipine (7.7 min).

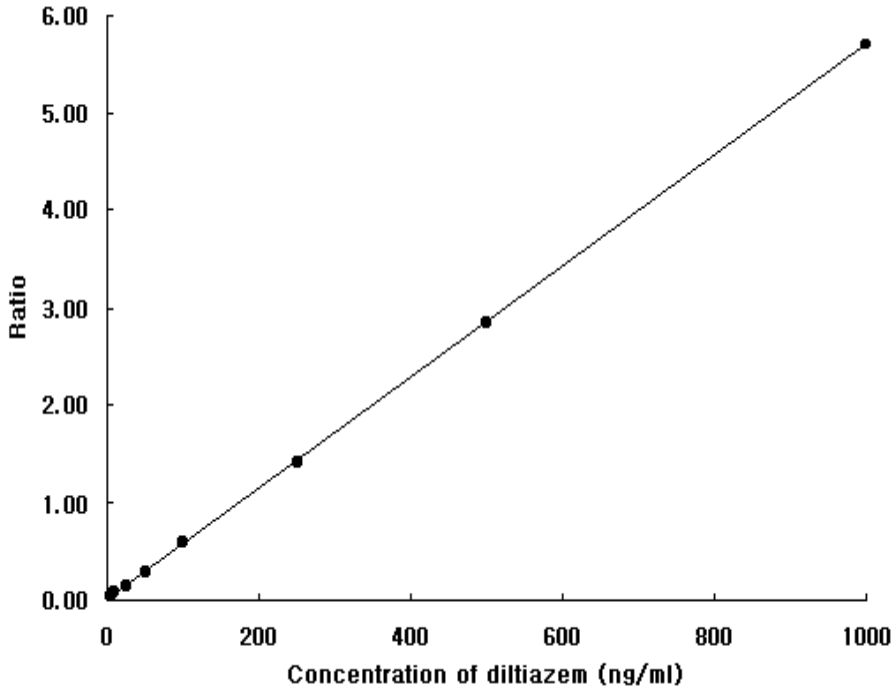

Figure 2. A calibration curve of nicardipine when spiked into the rat's blank plasma.

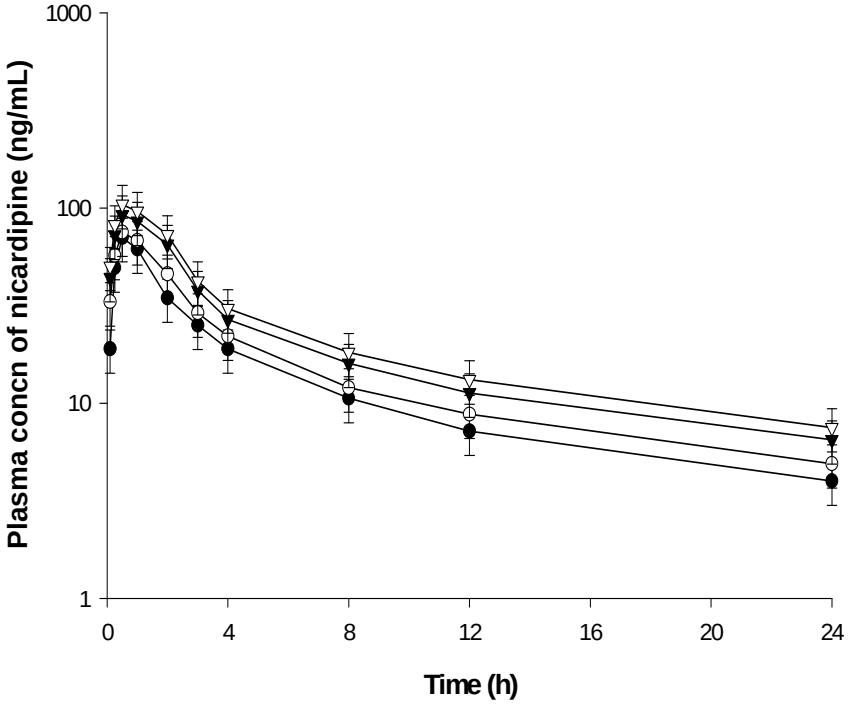

Figure 3. Mean plasma concentration–time profiles of nicardipine after oral administration of nicardipine (12 mg/kg) without (●) or with 0.6 mg/kg (○), 3 mg/kg (▼) and 12 mg/kg (▽) of EGCG to rats. Bars represent the standard deviation (n = 6).

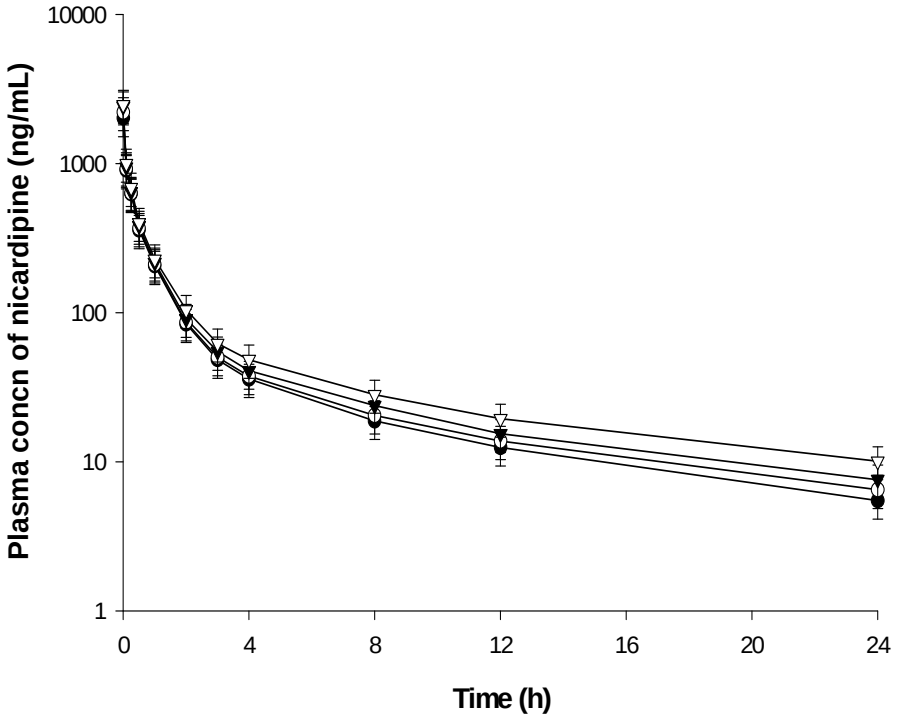

Figure 4. Mean plasma concentration–time profiles of nicardipine after i.v. administration of nicardipine (4 mg/kg) without (●) or with 0.6 mg/kg (○), 3 mg/kg (▼) and 12 mg/kg (▽) of EGCG to rats. Bars represent the standard deviation (n = 6).

Table 1. Mean plasma concentration of nicardipine after oral administration of nicardipine (12 mg/kg) presence or absence of EGCG to rats (Mean ± SD, n = 6).

Time (h)	Control	Nicardipine with EGCG		
		0.6 mg/kg	3 mg/kg	12 mg/kg
0	0	0	0	0
0.1	19.0 ± 3.4	33.1 ± 6.6	44.1 ± 9.3	50.2 ± 11.0
0.25	49.4 ± 8.9	57.1 ± 11.4	72.6 ± 15.2	82.1 ± 18.1
0.5	70.7 ± 12.7	75.2 ± 15.0	92.0 ± 19.3	104.3 ± 22.9
1	61.7 ± 11.1	68.1 ± 13.6	85.6 ± 18.0	96.2 ± 21.2
2	34.6 ± 6.2	46.0 ± 9.2	65.1 ± 13.7	73.1 ± 16.1
3	25.1 ± 4.5	29.0 ± 5.8	37.8 ± 7.9	42.3 ± 9.3
4	19.0 ± 3.4	22.1 ± 4.4	26.8 ± 5.6	30.5 ± 6.7
8	10.6 ± 1.9	12.0 ± 2.4	16.0 ± 3.4	18.2 ± 4.0
12	7.2 ± 1.3	8.8 ± 1.8	11.3 ± 2.4	13.2 ± 2.9
24	4.0 ± 0.7	4.9 ± 1.0	6.5 ± 1.4	7.5 ± 1.7

Table 2. Mean plasma concentration of nicardipine following intravenous administration of nicardipine (4 mg/kg) presence or absence of EGCG to rats (Mean ±SD, n = 6).

Time (h)	Control	Nicardipine with EGCG		
		0.6 mg/kg	3 mg/kg	12 mg/kg
0	2017 ± 363.1	2208 ± 441.6	2414 ± 506.9	2479 ± 545.4
0.1	903 ± 162.5	921 ± 184.2	942 ± 197.8	997 ± 219.3
0.25	625 ± 112.5	634 ± 126.8	645 ± 135.5	688 ± 151.4
0.5	358 ± 64.4	368.4 ± 73.7	382.6 ± 80.3	399.8 ± 88.0
1	206 ± 37.1	211.1 ± 42.2	216.5 ± 45.5	227.6 ± 50.1
2	84 ± 15.1	86.2 ± 17.2	90.9 ± 19.1	104.4 ± 23.0
3	48.4 ± 8.7	50.3 ± 10.1	54.8 ± 11.5	62.2 ± 13.7
4	36 ± 6.5	37.6 ± 7.5	40.8 ± 8.6	48.4 ± 10.6
8	18.8 ± 3.4	20.5 ± 4.1	23.8 ± 5.0	28.2 ± 6.2
12	12.5 ± 2.3	13.8 ± 2.8	15.4 ± 3.2	19.5 ± 4.3
24	5.5 ± 1.0	6.5 ± 1.3	7.6 ± 1.6	10.1 ± 2.2

Table 3. Mean (± S.D.) pharmacokinetic parameters of nicardipine after oral administration of nicardipine (12 mg/kg) presence or absence of EGCG to rats.

Paramater	Control	Nicardipine+EGCG		
		0.6 mg/kg	3 mg/kg	12 mg/kg
AUC (ng·h/mL)	371.0±66.8	443.1±79.8	579.5±115.9*	662.8±132.6**
C_{max} (ng/mL)	70.7±12.7	75.2±13.5	92.0±18.4*	104.3±20.9**
T_{max} (h)	0.5	0.5	0.5	0.5
CL/F (mL/min/kg)	32345±5822	27082±4874	20707±4141*	18106±3621*
$t_{1/2}$ (h)	9.5±1.7	9.9±1.8	10.4±2.1	10.6±2.1
R.B. (%)	100	119	156	179
A.B. (%)	11.0±2.1	13.2±2.5	17.2±3.3*	19.7±3.7**

Mean ± S.D. (n=6), * $P < 0.05$, ** $P < 0.01$, significant difference compared to the control

AUC: area under the plasma concentration–time curve from 0 h to infinity

C_{max}: peak plasma concentration

T_{max}: time to reach peak concentration

CL/F: total plasma clearance

$t_{1/2}$: half-life

A.B. (%): absolute bioavailability

R.B. (%) : relative bioavailability compared to the control group

Table 4. Mean (± S.D.) pharmacokinetic parameters of nicardipine after intravenous administration of nicardipine (4 mg/kg) presence or absence of EGCG to rats.

Paramater	Control	Nicardipine+EGCG		
		0.6 mg/kg	3 mg/kg	12 mg/kg
AUC(ng·h/mL)	1122±202.0	1189±214.0	1280±256.0	1460±292.0
CL_t(mL/min/kg)	3564±641.5	3365±605.7	3126±625.2	2740±548.0
$t_{1/2}$(h)	8.0±1.4	8.3±1.5	8.6±1.7	9.2±1.9

Mean ± S.D. (n=6)

AUC: area under the plasma concentration-time curve from time 0 to infinity

CL_t: total plasma clearance;

$t_{1/2}$: half-life

감사의 글

부족한 저를 항상 이끌어 주신 최준식 지도교수님께 감사드립니다. 심사를 해주신 한효경교수님과 범진필교수님께 감사를 드립니다. 지금까지 부족한 저를 인내와 사랑으로 이끌어 주신 부모님께 진심으로 감사를 드립니다. 그리고 논문에 도움을 주신 약제학교실원 여러분께도 무한한 감사를 드립니다. 앞으로 사회에 나가서 지금의 가르침을 바탕삼아 모든 일에 최선을 다하고 노력하는 약사가 되도록 하겠습니다.

졸업 후에는 많은 지도편달 부탁드리겠습니다.

저작물 이용 허락서

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논문제목	한글: 흰쥐에서 에피가로카테친이 경구 및 정맥으로 투여된 니칼디핀의 약물동태에 미친 영향 영문: Effects of epigallocatechin gallate on the pharmacokinetics of nicardipine after oral and intravenous administration of nicardipine in rats				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

– 다 음 –

1. 저작물의 DB 구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함.
2. 위의 목적을 위하여 필요한 범위 내에서의 편집・형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포・전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5 년으로 하고, 기간종료 3 개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1 개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음.
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송・출력을 허락함.

동의여부 : 동의 (√) 반대 ( )

2009 년 02 월

저작자: 임태환 (서명 또는 인)

조선대학교 총장 귀하