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The Pharmacokinetics of Nimodipine After Oral Administration in Rabbits with Hepatic Failure

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ABSTRACT – The pharmacokinetics of nimodipine, following a single 16 mg/kg oral dose, was investigated in rabbits with hepatic failure induced by 0.5 mL/kg (mild), 1.0 mL/kg (moderate) and 2.0 mL/kg (severe) of carbon tetrachloride (CCl_4 : olive oil=20 : 80, v/v). The plasma concentrations of nimodipine were determined by a high performance liquid chromatographic assay. The levels of sGOT and sGPT in rabbits with mild (86.2±29.0 and 98.5±33.1 unit/dL), moderate (168.1±61.2 and 196.2±66.0 unit/dL) and severe (292.7±82.2 and 314.2±99.8 unit/dL) hepatic failure were significantly increased compared to the control (38.0±10.1 and 32.4±10.2 unit/dL). The area under the plasma concentration-time curve (AUC) of nimodipine was significantly increased in mild (131.7±28.1%), moderate (168.8±32.8%) and severe (204.6±58.3%) carbon tetrachloride-induced hepatic failure rabbits compared to the control (100%) rabbits. The volume of distribution (V_d) and the total body clearance (CL_t) of nimodipine were significantly decreased in all hepatic failure groups. The elimination rate constant (K_{el}) of nimodipine was significantly decreased in moderate and severe carbon tetrachloride-induced hepatic failure rabbits. There was a correlation between sGOT ($y=1.01x+241$, $r=0.993$) or sGPT ($y=0.92x+243$, $r=0.997$) value and the AUC of nimodipine in the rabbits with hepatic failure. These findings suggest that the hepatic metabolism of nimodipine was inhibited by carbon tetrachloride-induced hepatic failure rabbits, resulting in the decrese in V_d and CL_t of nimodipine in the rabbits with mild, moderate and severe hepatic failure.

Key words – Nimodipine, Pharmacokinetics, Bioavailability, Hepatic failure

Nimodipine is a dihydropyridine calcium channel blocker which has been shown to selectively dilate cerebral arteries and increase cerebral blood flow in animals and humans.[1] Its major therapeutic indication is the prevention and treatment of delayed ischemic neurological disorders that often occur in patients with subarachnoid hemorrhages.[2,3] Nimodipine is rapidly absorbed after administered orally and widely distributed throughout the body. Nimodipine is subject to an extensive first-pass hepatic metabolism, resulting in a low systemic bioavailability.[4,5]

Since nimodipine is eliminated by the liver and undergoes significant first-pass metabolism, altered hepatic function might result in changes of intrinsic and systemic clearances of nimodipine, as well as bioavailability.[6-8] Although liver diseases can alter the pharmacokinetic characteristics of drugs with high extraction ratio, pharmacokinetic studies of the effects of hepatic disorders on the disposition of nimodipine have not been reported.

The aim of this study was to investigate the effect of hepatic failure induced by carbon tetrachloride on the bioavailability of nimodipine after oral administration to rabbits.

Materials and Methods

Materials and reagents

Nimodipine and the internal standard, nitrendipine, were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Ethyl acetate and methanol were purchased from Merck Co. (Darmstadt, Germany). Peppermint oil was purchased from the Junsei Co. (Tokyo, Japan). The other chemicals were of reagent grade and used without further purification. The apparatuses used for the study are as follow: HPLC (Model LC-10A, Shimadzu Co., Kyoto, Japan) and a syringe pump (Model 341B, Sage Co., Kyoto, Japan).

Animal experiments and drug administration

White male New Zealand rabbits weighing 2.0-2.4 kg were fasted for at least 36 h prior to the experiment and were given water ad libitum. The rabbits were placed under 25% urethane (4 mL/kg) anesthesia and the right femoral artery was cannulated with polyethylene tubing (PE-50, Intramedic, Clay

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Adams, USA) for blood sampling at room temperature. These experiments were performed in accordance with the "Guiding Principles in the Use of Animals in Toxicology" that were adopted by the Society of Toxicology (USA) in July 1989 and revised in March 1999. The animal care committee of our institution (Chosun University) approved this study.

Mild, moderate and severe hepatic failure were induced by subcutaneous injection of 0.5 mL/kg, 1.0 mL/kg and 2.0 mL/kg carbon tetrachloride (CCl_4 : olive oil=20 : 80, v/v) to rabbits at 24 h prior to the experiment, respectively. Nimodipine, 16 mg/kg (32 mg dissolved in 10 mL peppermint oil), was administered orally to the rabbits. Blood samples (1.5 mL) were drawn from at 0, 0.1, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h after dosing. The blood samples were centrifuged at 3,000 rpm for 10 min and the plasma samples (0.5 mL) were stored at −70°C until analysis.

HPLC Assay

The plasma nimodipine concentrations were determined by an HPLC assay with a modification of the method repored by Qian *et al.*[9] Briefly, 50 μL of nitrendipine (1 μg/mL), as the internal standard and 50 μL of ethyl acetate were added to 0.5 mL of the plasma samples. The mixture was then stirred for 10 min and centrifuged at 3,000 rpm for 10 min. 5 mL of the organic layer were transferred and evaporated at 40 under a stream of nitrogen gas. The residue was then dissolved in 300 μL of 65% methanol and centrifuged at 3,000 rpm for 10 min, and 50 μL of the supernatant was injected into the HPLC system.

The HPLC system consisted of two solvent delivery pumps (Model LC-10AD, Shimadzu Co., Japan), a UV detector (Model SPD-10A), a system controller (Model SCL-10A), degasser (Model DGU-12A) and a autoinjector (SIL-10AD). The UV detector was set at a wavelength of 310 nm. The stationary phase used was a Hypersil ODs column (5 μm, 4.6× 150 mm). The mobile phase consisted of methanol : water (65 : 35, v/v). The retention times at a flow rate of 1.0 mL/min were 7.6 min and 9.1 min for internal standard and nimodipine, respectively. The calibration curve was obtained for the concentration range of 10 ng/mL to 1000 ng/mL and regression equation was $y=206.0x+18.1$ ($r=0.999$).

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed LARGAN computer program.[10] The area under the plasma concentration-time curve from time zero to infinity (AUC) was computed using the LAGRAN method in order to reduce the errors associated with the trapezoidal rule. The peak plasma concentration (C_{max}) and the time to reach the peak plasma concentration (T_{max}) were determined by a visual inspection of the experimental data. The elimination rate constant (K_{el}) was estimated from the terminal slope, and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. The total body clearance (CL_t) and the volume of distribution (V_d) were obtained by (Dose×F)/AUC and (Dose×F)/(K_{el}×AUC). The absolute bioavailability (F) was calculated using $(AUC_{oral}/AUC_{iv})\times(Dose_{i.v}/Dose_{oral})$ and the relative bioavailability ($F_{R.B}$ %) of nimodipine was estimated by $(AUC_{hepatic\ failure}/AUC_{control})\times 100\%$.

Statistical analysis

Data were presented as mean±standard deviation. An unpaired Student's t-test was used to determine any significant differences among the control group and hepatic failure groups. A p value<0.05 was considered to be significant.

Results and Discussion

Clinical laboratory data in carbon tetrachloride-induced hepatic failure rabbits were shown in Table I. The level of sGOT, sGPT and ALP in all carbon tetrachloride-induced hepatic failure rabbits were significantly increased ($p<0.01$), compared to the control rabbits. Bilirubin levels in moderate and severe hepatic failure rabbits were significantly increased ($p<0.05$), compared to the control rabbits. The mean plasma concentration-time profiles and estimated parameters of nimo-

Table I–*Laboratory Data in Control Rabbits and Rabbits with Mild, Moderate, and Severe Hepatic Failure Induced by Carbon Tetrachloride*

Parameters	Control	Hepatic failure		
		Mild	Moderate	Severe
sGOT (unit/L)	38.0±10.1	86.2±29.0**	168.1±61.2**	292.7±82.2**
sGPT (unit/L)	32.4±10.2	98.5±33.1**	196.2±66.0**	314.2±99.8**
ALP (unit/L)	95.0±34.0	151.3±48.0**	218.4±72.0**	361.8±92.3**
Bilirubin (mg/dL)	0.30±0.081	0.42±0.160	0.55±0.181*	0.68±0.192*

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

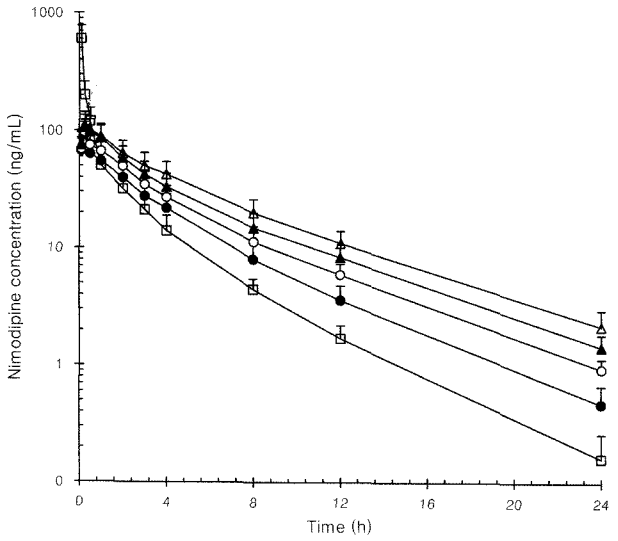

Figure 1–Mean plasma concentration of nimodipine after oral administration (16 mg/kg) in rabbits with normal liver function(●) and mild(○), moderate(▲), and severe(△), hepatic failure induced by carbon tetrachloride and after i.v. administration in rabbits with normal liver function (□, 2 mg/kg). The bars represent standard deviation (n=6).

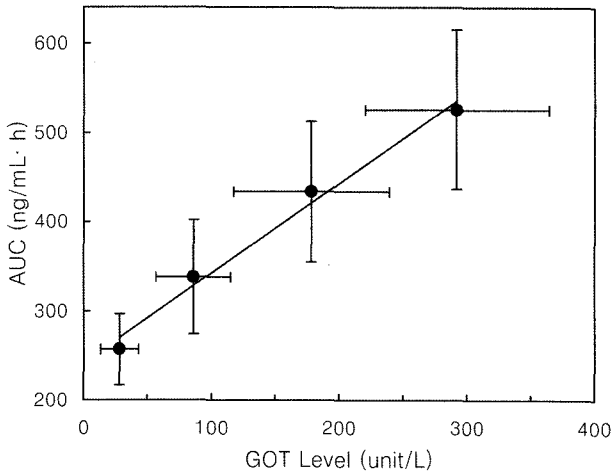

Figure 2–Correlation between GOT level and AUC. y=1.01x+241 (r=0.993). The bars represent standard deviation (n=6).

dipine after oral administeration to rabbits with hepatic failure were shown in Figure 1 and Table II, respectively.

The AUC of nimodipine was significantly increased in mild (338.9±74.4 ng/mL·h), moderate (434.4±89.1 ng/mL·h) and severe (526.6±99.8 ng/mL·h) failure rabbits compared to the control rabbits (257.4±68.4 ng/mL·h). The T_{max} in severe hepatic failure rabbit was significantly ($p<0.05$) longer than that in the control rabbits. The K_{el} values in moderate and severe hepatic failure rabbits were significantly ($p<0.05$, respectively) lower than that in the control rabbits. The CL_t of nimodipine was significantly increased in rabbits with mild (4.97±0.87 L/h/kg), moderate (3.87±1.10 L/h/kg) and severe (3.13±0.76 L/h/kg) hepatic failure, compared to the control rabbits (6.53±1.78 L/h/kg). The V_d of nimodipine in all groups of hepatic failure were significantly ($p<0.01$ and $p<0.05$, respectively) lower than that in the control rabbits. The absolute bioavailability (F) and the relative bioavailability ($F_{R.B}$%) of nimodipine in the rabbits with hepatic failure were significantly higher (0.14-0.22 and 131.7-204.6%, respectively) than that in the control rabbits (0.11 and 100%), respectively. There was a correlation between the sGOT (y=1.01x+241, r=0.993) or sGPT (y=0.92x+243, r=0.997) value and

Table II–*Pharmacokinetic Parameters of Nimodipine After Oral Administration of Nimodipine (16 mg/kg) in Control Rabbits and Rabbits with Mild, Moderate and Severe Hepatic Failure Induced by Carbon Tetrachloride*

Parameters	Control 16 mg/kg	Hepatic failure			I.V 2 mg/kg
		Mild	Moderate	Severe	
C_{max} (ng/mL)	91.2±26.4	96.8±19.8	105.3±35.3	118.7±29.1	-
T_{max} (min)	17.5±5.5	20.0±6.1	22.5±4.9	25.0±5.4*	-
AUC (ng/mL·h)	257.4±68.4	338.9±74.4*	434.4±89.1**	526.6±99.8**	301.4±79.5
K_{el} (h^{-1})	0.181±0.034	0.162±0.035	0.148±0.049*	0.142±0.055*	0.199±0.033
$T_{1/2}$ (h)	3.83±0.99	4.28±1.24	4.68±1.11	4.88±0.97	3.51±0.77
CL_t (L/h/kg)	6.53±1.78	4.97±0.87*	3.87±1.10**	3.13±0.76**	6.64±1.47
V_d (L/kg)	30.2±9.4	27.1±3.11*	23.2±5.4**	19.4±4.2**	136.9±39.7
F	0.11±0.02	0.14±0.03*	0.18±0.03**	0.22±0.04**	1.00
$F_{R.B}$ (%)	100.0	131.7±28.1*	168.8±32.8**	204.6±58.3**	-

Mean±S.D. (n=6), *$p<0.05$, **$p<0.01$, significant difference compared to control.
C_{max} : peak concentration; T_{max} : time to reach peak concentration; AUC : area under the plasma concentration-time curve from time zero to infinity; K_{el} : elimination rate constant ; $t_{1/2}$: terminal half-life; CL_t : total body clearance; F : absolute bioavailability compared to AUC of I.V. administration; $F_{R.B}$: relative bioavailability compared to AUC of control.

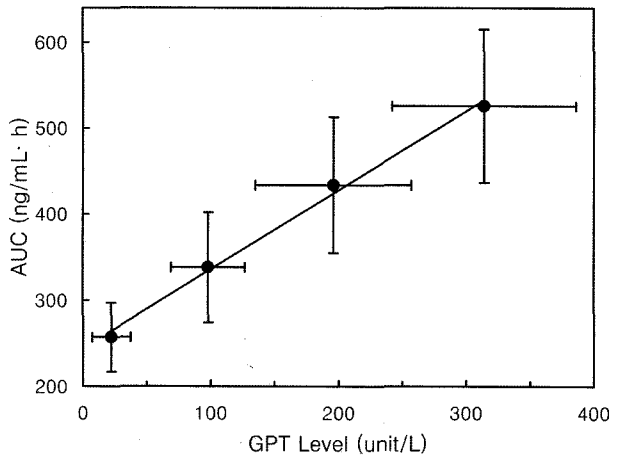

Figure 3–Correlation between GPT level and AUC. y=0.92x+243 (r=0.997). The bars represent standard deviation (n=6).

the AUC of nimodipine in the rabbits with hepatic failure.

In spite of the high intra- and inter-subject variability of calcium channel blockers,[11,12] their therapeutic efficacy and safety are not critically dependent on pharmacokinetic variability because of wide therapeutic window.[13] Due to extensive hepatic first-pass metabolism of nimodipine induction of hepatic failure is expected to reduce total systemic clearance and increase the oral bioavailability of nimodipine. Pharmacokinetics of verapamil, other calcium channel blocker, in control subjects were compared with patients with biopsy-confirmed liver disease after a single intravenous does.[14] The subjects with liver dysfunction showed a 3-fold and a 1.7-fold decrease in systemic clearance and apparent volume of distribution, respectively, with a corresponding increase of plasma half-life. Somogyi *et al.*[15] evaluated the disposition and bioavailability of verapamil, in patients with histological proven hepatic cirrhosis and reported the changes in pharmacokinetic parameters. The oral and systemic clearance were reduced by 5- and 2-fold, respectively. An increase of terminal plasma half-life from 3.7 to 14.2 hours was also reported along with higher peak drug concentrations and a significant increase in systemic bioavailability (22.0% vs 52.3%).

These observations support the conclusion that metabolism of nimodipine in the liver may decreased due to the suppressed hepatic function in carbon tetrachloride-induced hepatic failure. Based on our results, it is suggested in patients with liver disease, doses modification of nimodipine should be considered according to the degree of hepatic failure.

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