Pharmacokinetics and Pharmacodynamics of Intravenous Diltiazem in Dogs

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= Abstract =The pharmacokinetic and cardiovascular effects of dilitiazem were studied in six adult dogs after intravenous infusion of diltiazem HCl over a period of 10 minutes. Plasma drug concentrations, P-R intervals on EKG, blood pressure and heart rate changes were serially measured upto six hours after drug administration. To analyze the effect site concentration-effect relationships of diltiazem, plasma drug concentrations and response data were fitted to a three-compartment pharmacokinetic/pharmacodynamic model with NON-LIN program. Plasma diltiazem levels peaked at 743.1 $\pm$ 224.6 ng/ml in about 1 mg/kg dose in four dogs, 1151.5 ng/ml in 1.43 mg/kg dose and 1177.4 ng/ml in 1.85 mg/kg dose and thereafter decreased triexponentially. The terminal half-life estimated was 2.0 $\pm$ 0.5 hours, and the volume of distribution at steady-state(Vdss) and the total body clearance were 4.42 $\pm$ 0.87 L/kg and 25.5 $\pm$ 6.6 L/hr, respectively. After intravenous diltiazem, the P-R interval increased upto 27.79 $\pm$ 12.48% in about 1.0 mg/kg, and 34.25% in 1.43 mg/kg and 45.42% in 1.85 mg/kg dose. Diastolic blood pressure decreased upto 16.75 $\pm$ 8.26% in about 1 mg/kg, 19.69% in 1.43 mg/kg and 30.45% in 1.85 mg/kg dose. Counterclockwise hysteresis curve was found in the P-R interval prolongation vs. the plasma dilitiazem concentration curve. The P-R interval prolongation-effect site concentration relationship was best explained by the linear model except for one dog, in which Emax model was best applied. The estimated equilibration rate constant(keo) between plasma and effect site was 0.46 $\pm$ 0.33 min^{-1}, and slope for the linear model was 0.063 $\pm$ 0.002. Emax and EC$_{50}$ were estimated as 99 msec and 667 ng/ml in one dog. The blood pressure-effect site concentration relationship was best fitted by a linear model in all six dogs, and the estimated keo and slope of the relationship were >1 min^{1} and 0.069 $\pm$ 0.042, respectively.

Key Words: *Diltiazem, Pharmacokinetics, Pharmacokinetic-Pharmacodynamic analysis, Dog*

INTRODUCTION

Diltiazem(*d*-cis-3-acetoxy-2,3-dihydro-5-[2-(dimethyl-amino-ethyl]-2-(p-methoxy-phenyl)-1,5-benzothiazepine-4(5H)-one) is a calcium channel blocker that differs in chemical structure from earlier blockers such as

pehnylalklamine group(e.g., verapamil) and dihydropyridine group(e.g., nifedipine) of compounds. The myocardial depressant activity of diltiazem has been found to be less than that of verapamil, but its effect on the freqency of heart beat has been reported stronger than on the contractile force (Pe'rez *et al.*, 1982). Though the vascular relaxant potency is less than that of the dihydropyridines(Zweiten and Timmermans, 1983), it is also potent vasodilators useful in the treatment of angina pectoris (People *et al.*, 1981; Feldman *et al.*, 1982; Hossack *et al.*, 1982), systemic hypertension (Safar *et al.*, 1983), pulmonary hypertension (Crevey *et al.*, 1982), hypertropic cardiomyopathy(Nagao *et al.*, 1981) and even severe congestive heart failure (Joyal *et al.*, 1986). Its suppressive effects on the atrioventricular (AV) node have also enabled it to be used for the management of supraventricular tachycardia(Rozanski *et al.*, 1982; Betriu *et al.*, 1983).

The cardivoascular effects of each of calcium channel blockers vary depending on the route of administration and the extent of left ventricular dysfunction(Philip *et al.*, 1985). Intravenous dilitiazem can produce prompt reduction of blood pressure and both systemic and coronary resistance, which elicits a reflex increase in heart rate and cardiac output (Joyal *et al.*, 1986). Heart rate then falls below initial levels due to the direct negative chronotropic effect of diltiazem. By these actions, intravenous dilitiazem has shown promise for the prompt management of cardiovascular diseases. such as acute episode of paroxysmal supraventricular tachycardia (PSVT) and angina (Rozanski *et al.*, 1982). However, inconsistent results have been reported on the hemodynamic effects of IV diltiazem for heart rate and stroke volume (Bertrand *et al.*, 1982; Dash *et al.*, 1984; Safar *et al.*, 1983; Kenny *et al.*, 1984), partly caused by variences in the dosing schedule and lack of data on plasma drug concentrations (Joyal *et al.*, 1986). A few data have shown the plasma concentration and cardiovascualr response relationship of diltiazem(Fu *et al.*, 1986; Smith *et al.*, 1983). However, these data lacked the quantitative analysis of the dose-concentration-cardiovascular effect relationships.

Since Sheiner et al.(1979) proposed the simultaneous pharmacokinetic and pharmacodynamic model which described the biophase drug concentration-effect relationship even in a non--steady-state condition, some drugs have been used analyzing dose-concentration-response relationships with this model (Kleinbloesem *et al.*, 1985; Piergies *et al.*, 1987). The present study was performed in order to analyze the precise relationship between the simulated effect site drug concentration and cardiovascular effects of IV diltiazem.

METHODS

Animals and Experimental Procedure: Six adult dogs weighing 9.5-12.5 kg were used. All the dogs were anesthetized with a loading dose of sodium pentobarbital(25 mg/kg intravenously) followed by the continuous infusion of maintenance doses 2-3 mg/kg/hr mixed with normal saline throughout the experiment. Regular artificial respiration was performed with a Harvard respirator connected to the endotracheal tube. An angiocatheter(18 G) with a heparin lock was placed within a femoral artery, which was connected to a pressure transducer which permitted blood sampling and monitoring of systemic blood pressure and heart rate. Another angiocathether(21 G) was inserted into a peripheral vein in the foreleg for the infusion of diltiazem HCl or normal saline to maintain a constant urine flow. A Foley catheter(6 F) was also indwelled in the urinary bladder for the collection of urine. Lead II electrocardiogram was recorded on a polygraph (Devices Instrument Co., England) at a paper speed of 100 mm/sec to measure P-R interval changes. After achieving a state of constant anesthesia, with five consecutive measures of control blood pressure, heart rate and P-R intervals, diltiazem HCl of 0.96-1.85 mg/kg dose was infused with a Sage infusion pump over a period of 10 minutes. Serial blood samples were drawn at 0 times. 3, 5, 7, 10, 11, 12, 13, 15, 17, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes through an indwelled catheter placed within the femoral artery. Concomitantly, changes of P-R intervals on the EKG, blood pressure and heart rate were measured serially. Blood samples were centrifuged to separate plasma immediately. Plasma and urine samples were stored at -20℃ until subsequent analysis.

Measurement of Plasma and Urine Ditiazem

Concentration: Plasma and urine concentrations of diltiazem were measured by modification of the HPLC method of Montamat et al. (1987). For the extraction of diltiazem from plasma or urine, 4 ml of hexane-isoamylalcohol (98:2) were added to each polypropylene tube containing 2 ml of plasma or urine sample and 100 ul of carbonate buffer (pH 9.0). The tubes were agitated vigorously for 10 minutes and centrifuged at 4℃ for 10 minutes at 400 G. The organic layer was transferred to another tube which contained 200 ul of 0.01 N HCl and the procedure was repeated. The tubes containing a total of 7 ml of organic matter(from the first and second extractions) and 0.01 N HCl were then agaitated for 10 minutes and centrifuged at 4℃ for 10 minutes at 400 G. The upper organic layer was discarded, and 100 ul aliquot of the lower aqueous phase was injected directly into the sample loop. Chromatographic analysis was done by the HPLC system using Gilson model 302 pump, variable UV detector (Gilson, France) set at 230 nm with C-R 6A chromatopac integrator (Shimatzu, Japan) and six-port rotary valve injector (Model 7161, Rheodyne, Berkerley Co, USA) with a 100 ul sample loop. The chromatographic separations were achieved using a reverse phase, C_{18} μ Bondapak Column (25 cm × 4.6 mm ID, 5 μm particle size, Gilson, France) with 60 mM phosphate buffer -acetonitril(60:40) added 5 mM triethylamine as a mobile phase. The solvent flow rate was 1.0 ml/min. Under these conditions, the retention times of diltiazem and internal standard, diphenhydramine, were 9.8 and 11.7 minutes, respectively (Fig. 1). A plot of the height ratio of diltiazem and internal standard was linear in the range 10 to 2.000 ng/ml. The measurement limit for routine analysis was 5 ng /ml. The analytic recovery for routine analysis of diltiazem was above 90%, and the interassay coefficient of variation was estimated to be under 6.5%.

Pharmacokinetic Analysis: To analyze the plasma concentration time course after the intravenous infusion of diltiazem, compartmental analysis was performed. The following functions were fitted to plasma diltiazem concentration (C_p) by weighted nonlinear regression analysis using NONLIN package (Metzler, 1984); $C_p = Ae^{-\lambda_1 \cdot t} + Be^{-\lambda_2 \cdot t} + Ce^{-\lambda_3 \cdot t}$
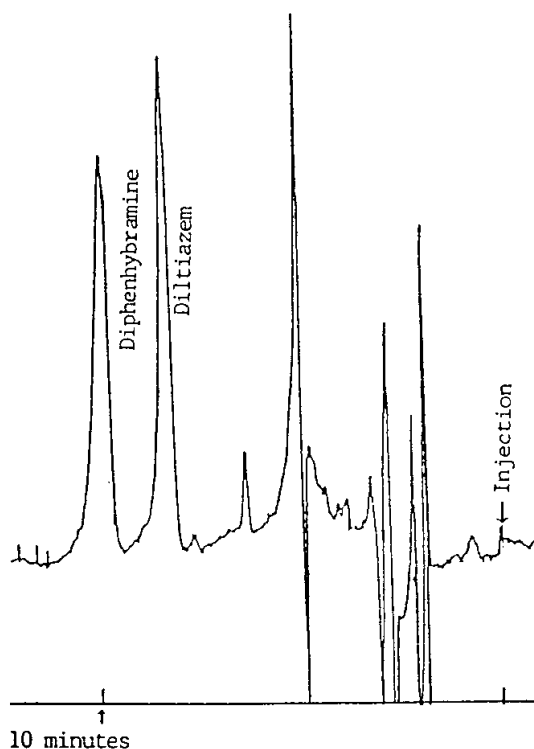
where A,B and C are hybrid intercept terms and

Fig. 1. Chromatogram obtained after injection of extracted plasma sample of diltiazem 100ng/ml and internal standard, diphenhydramine.

λ_1, λ_2 and λ_3 are hybrid coefficients representing the rate constants of initial two distribution phases and terminal elimination phase. In the fitting procedure, the residuals were weighted with the inverse of the observed values, because the error of the assay is a more or less constant percentage of the concentration. The terminal half-life($t_{1/2\beta}$) of diltiazem was calculated from the following equation:

$$t_{1/2\beta} = 0.693/\lambda_3 \qquad (1)$$

Fast and slow intercompartmental clearances (Cl_F and Cl_S) in the model used (Fig. 2) were obtained from the product of volume of distribution and the corresponding intercompartmental transfer rate constant according to the equations (Perrier and Gibaldi, 1974):

$$Cl_F = k_{12} V_C = k_{21} V_F \text{ or}$$
$$Cl_S = k_{13} V_C = k_{31} V_S \qquad (2)$$

where, V_s and V_F represent the peripheral distribution volume of the fast and slow compart-

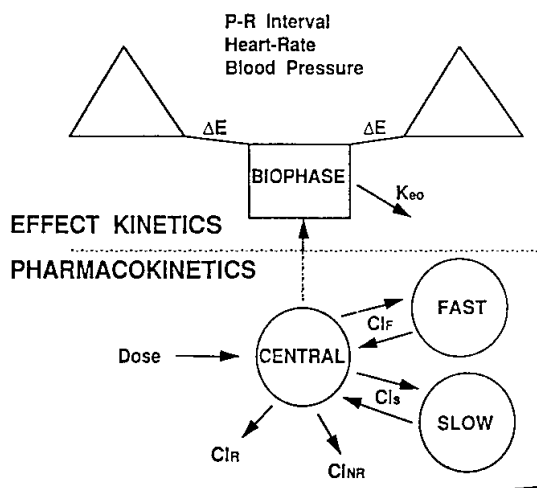**Fig. 2.** General Pharmacokinetic/Pharmacodynamic model for diltiazem biophase concentration-response analysis; keo, disposition rate constant from biophase; ΔE, unit change of PR interval, heart rate or BP according to the changes of diltiazem level in biophase.

ments. Renal clearance (Cl_R) of diltiazem was calculated from the amount excreted unchanged during the experimental period$(Ar_{o \to t})$ divided by the area under the plasma diltiazem concentration (AUC) during that time period:

$$Cl_R = \frac{Ar_{o-t}}{AUC_{o \to t}} \tag{3}$$

where, AUC was estimated by standard linear/log trapezoidal rule.

Analysis of Pharmacokinetic-Pharmacodynamic Relationship: Fig. 2 shows a simultaneous pharmacokinetic/pharmacodynamic model which describes the relationships of dose-plasma concentration-effect site concentration-cardiovascular effects of diltiazem. Assuming a negligible amount of diltiazem is transferred to the effect site from the pharmacokinetic phase and the partitioning coefficient between these two phases is 1, the effect site diltiazem concentration(Ce) can be obtained by the function with conventional pharmacokinetic parameters and keo(disposition rate constant from the effect site). To analyze the relationship between the effect site diltiazem concentration and cardiovascular effects, we used Emax or linear model of pharmacodynamics. According to the Emax model, diltiazem effect would show the

hyperbolic relationship to the concentration:

$$E = \frac{E_{max} \, Ce}{EC_{50} + Ce} + E_O \tag{4}$$

where, E is the magnitude of drug response, Ce is the effect site diltiazem concentration, Emax is the maximum effect attributable to diltiazem and EC_{50} is the concentration producing 50% of Emax. Another model used is the linear model in which the effect is proportional to the drug concentration:

$$E = \alpha \cdot Ce + Eo \tag{5}$$

where, α is the slope of the line relating the effect to the concentration and Eo is the baseline response.

To obtain parameters describing the time course of the drug concentration and the relationships of biophase drug concentration-cardiovascular effects, such as keo, E_{max}, EC_{50} and slope(α) of the linear model, the Ce(t) functions from equation and the pharmacodynamic function were simultaneously fitted with the plasma diltiazem concentration data and cardiovascular effect data by weighted nonlinear regression. In our study, P-R interval prolongation and pressure change data were fitted to the corresponding functions. The time to reach 50% equilibrium between the effect site and the plasma pool($t_{1/2eq}$) was also calculated from the parameter of keo:

$$t_{1/2eq} = 0.693/keo \tag{6}$$

RESULTS

The plasma diltiazem concentration-time course after a 10 minute infusion was best explained by three exponential terms suggesting that a three-compartmental model would be appropriate for describing the kinetics(Fig. 3). After a 10-minute intravenous infusion of diltiazem, plasma levels peaked at 743.1 ± 224.6 ng/ml in about 1 mg/kg dose in four dogs, 1151.5 ng/ml in 1.43 mg/kg dose, and 1177.4 ng/ml in 1.85 mg/kg dose in one dog. Thereafter, plasma drug concentrations decreased multiexponentially. The pharamacokinetic parameters of diltiazem in six dogs are given in Table 1. The mean volume of distribution at steady-state(Vdss) in six dogs was 4.42 L/kg, and the central compartment volume of distribution varied widely with range of 0.08 to 0.51 L/kg. Total body clearance was 25.5 ± 6.6 L/hr, and

Table 1. Pharmacokinetic parameters of diltiazem after intravenous infusion over 10 minutes in dogs.

Dog No.	Dose* (mg/kg)	V_C (L/kg)	V_F (L/kg)	V_S (L/kg)	$t_{1/2\beta}$ (h)	Cl (L/h)	Cl_F (L/h)	Cl_S (L/h)	Cl_R (L/h)
1	1.0	0.08	0.49	4.17	2.17	22.1	54.6	37.4	0.170
2	0.96	0.51	1.34	2.01	1.93	24.6	161.9	11.9	0.025
3	1.1	0.30	1.37	2.53	1.20	38.6	205.6	14.5	0.045
4	1.43	0.14	0.73	4.86	2.77	24.7	65.4	29.0	0.008
5	1.14	0.20	0.88	2.14	1.96	20.4	148.3	21.3	0.121
6	1.85	0.30	1.41	3.16	1.99	22.8	73.8	27.4	0.006
Mean		0.25	1.04	3.13	2.00	25.5	118.1	23.6	0.063
S.D.		0.15	0.39	1.15	0.50	6.6	61.9	9.6	0.068

* Doses were obtained from actual measurement of administered amount of diltiazem.

* V_c: central compartment volume, V_F; fast peripheral compartment volume, V_s; slow peripheral compartment volume, $t_{1/2\beta}$: terminal half life, Cl: total body clearance, Cl_F: fast intercompartmental clearance, Cl_s: slow intercompartmental clearance, Cl_R: renal clearance of diltiazem
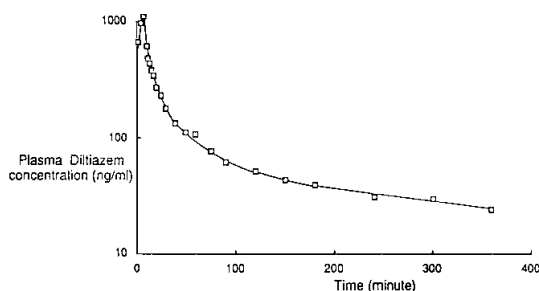

Fig. 3. Representative plasma diltiazem concentration vs. time profile after intravenous infusion of diltiazem 15mg, over 10minutes to Dog No. 4. Three phasic decay was noted in the concentration - time curve.

the renal clearance was corresponded to 0.25% of the total body clearance. Only 0.03 to 0.66% of the diltiazem administered was excreted in an unchanged form during the six hour experimental period. The mean terminal half-life $(t_{1/2}\beta)$ was 2.0 ± 0.5 hours. Based on a three-compartment model for IV diltiazem (Fig. 2), the intercompartmental clearances between the central and peripheral compartments were 118.1 ± 61.9 L/hr (Cl_F) and 23.6 ± 0.6 L/hr (Cl_S), respectively.

The average baseline P-R interval in the experimental dogs was 144.1 ± 12.5 msec. After an intravenous infusion of diltiazem, the P-R interval increased upto 27.79 ± 12.48% in four dogs administered about 1 mg/kg, 34.25% in 1.43 mg/kg and 45.42% in 1.85 mg/kg dose of diltiazem. Maximum prolongation was observed immediately after the stop of the 10-minute infusion (about 1.5 minutes after the end of the infusion), and lagged shortly behind the peak plasma diltiazem level (Fig. 4). However, there was a definite counterclockwise hysteresis in the curve of the P-R interval prolongation vs. the plasma diltiazem concentration (Fig. 5).

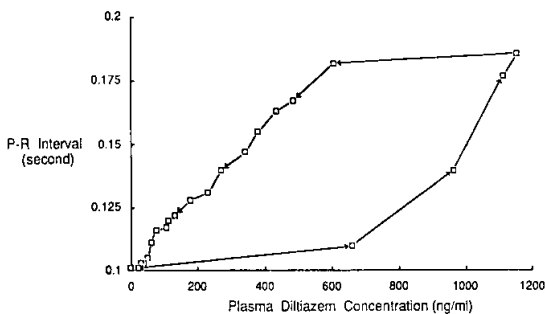The linear model(eq. 5) was best fitted as the

Fig. 4. Representative plotting of plasma diltiazem concentration against P-R interval after intravenous infusion of diltiazem 15mg to Dog 4. Arrows indicate the time-course of the plasma concentration-effect relationships. Anticlockwise hysteresis was noted.
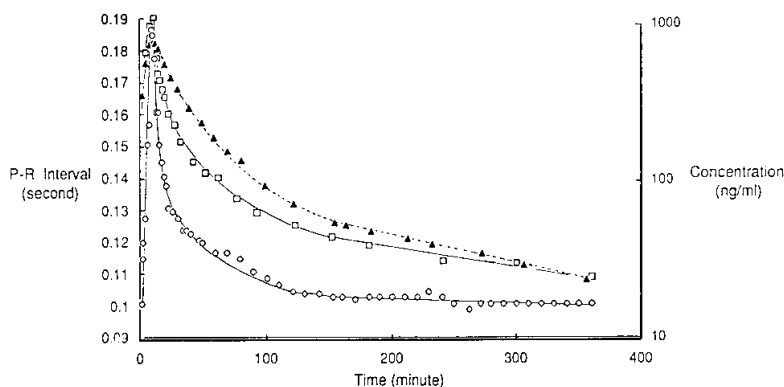
Fig. 5. Representative plotting of P-R interval(○) and plasma concentration of diltiazem(□)after intravenous infusion of diltiazem 15mg over 10 minutes to Dog No. 5. Effect site concentrations(▲) were simulated from the pharmacokimetic/pharmacodynamic model.

optimum pharmacodynamic model for linking the biophase diltiazem concentration and the cardiovascular effects of the P-R interval prolongation in five out of six dogs except for Dog. 6, in which the Emax model(eq. 4) was more appropriate(Fig. 6). The disposition rate costant (keo) from biophase was $0.46 \pm 0.33 \, \text{min}^{-1}$, and the mean equilibration half-life into biophase($t_{1/2eq}$) was 1.73 min. The slope for the relationship of the effect site diltiazem concentration and the P-R interval prolongation was 0.063 ± 0.002 in five dogs(Table 2). In Dog 6, the maximum P-R
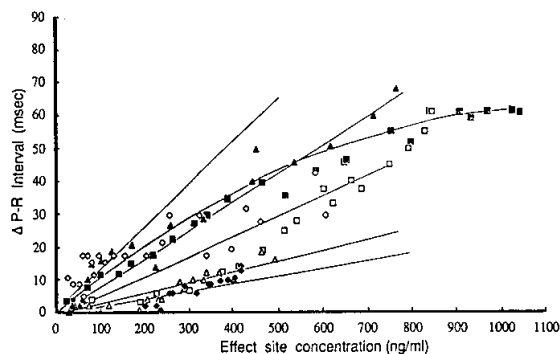

Fig. 6. Relationships of pharmacodynamic effect(P-R interval change) and effect site concentration of diltiazem after intravenous infusion of diltiazem HCl. Data were best fitted to linear model of concentration-effect relationship, except those of Dog 6(■) which were best explained by E-max model.

interval prolongation effect(Emax) was 99 msec, and the concentration producing 50% of Emax(EC$_{50}$) was 667 ng/ml.

Diastolic blood pressure was decreased upto $16.75 \pm 8.26\%$ in four dogs administered about 1.0 mg/kg (control diastolic pressure; 95.2 ± 20.5 mmHg), 19.69% in 1.43 mg/kg and 30.45% in 1.85 mg/kg dose of diltiazem(Fig. 7). The curve of plasma diltiazem concentration against diastolic blood pressure changes showed a less pronounced counterclockwise hysteresis compared to the curve of the P-R interval prolongation, suggesting more rapid euqilibrium between plasma and biophase.

For the blood pressure data, especially that of diastolic pressure, the linear model was best for the pharmacokinetic-dynamic link in all six dogs. The mean value of keo was $>1.0 \, \text{min}^{-1}$, and the slope(α) of the effect site diltiazem concentration-diastolic blood pressure relation was 0.069 ± 0.042(Table 2). The equilibration half-life($t_{1/2eq}$) for the blood pressure effect was lesser than 1min.

DISCUSSION

After intravenous infusion of diltiazem HCl over 10 minutes, plasma drug concentrations decreased triexponentially in all six dogs (Fig. 3) and were best fitted to the three-compartment model(Fig. 2). For the pharmacokinetic study of diltiazem, two-or three-compartment were frequently used in several previous reports. Herman et al. (1983) used a two-compartment mod-

Table 2. Pharmacokinetic/pharmacodynamic relationships of intravenous diltiazem

Dog No.	P-R interval and Biophase concentration relationship		Blood Pressure and Biophase concentration relationship	
	keo(min $^{-1}$)	α	Keo(min $^{-1}$)	α
1	0.20	0.076	0.17	0.107
2	0.27	0.044	>2.0	0.122
3	1.02	0.045	>2.0	0.089
4	0.18	0.092	1.85	0.026
5	0.68	0.057	1.36	0.035
6	0.45	*	1.13	0.035
Mean	0.46	0.063	>1.0	0.069
S.D.	0.33	0.002		0.042

* Best fitted by Emax model of pharmocokinetic/pharmocodynamic relationship; calculated Emax and EC_{50} were 99 msec and 667ng/ml, respectively.

** keo: equalibrium rate constant into the effect site,
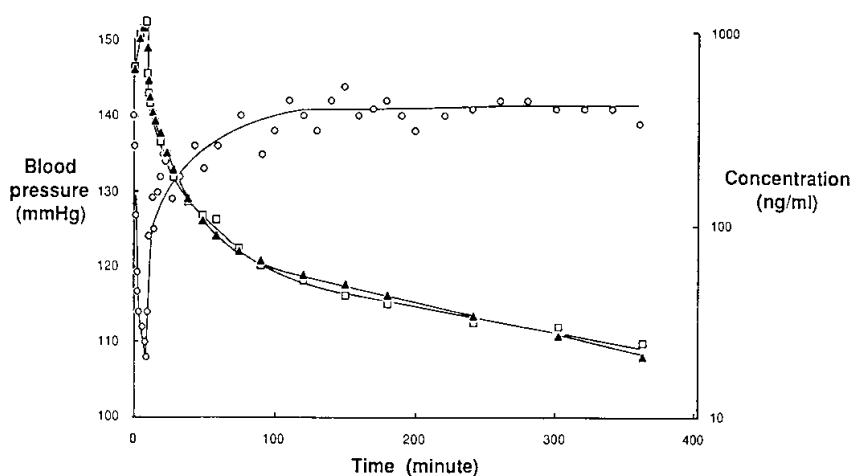　　α : slope of the linear model.

Fig. 7 Representative plotting of diastolic blood pressure(○) and plasma concentration of diltiazem(□) after intravenous infusion of diltiazem 15mg over 10 minutes to Dog No. 4. Effect site concentrations(▲) were simulated from the pharmacokinetic/pharmacodynamic model.

el in a study of healthy human volunteers, but the other reporters used a three-compartment open model to explain the plasma concentration-time course after intravenous administration of diltiazem(Smith *et al.*, 1983; Ochs and Knüchel, 1984). The terminal half-life($t_{1/2\beta}$) was 2.0 ± 0.5 hours in six dogs of our study. In hu-

mans, however, the terminal half-lives reported were greater than that of our result in dogs. After intravenous infusion of diltiazem in humans, $t_{1/2\beta}$ have been estimated to be 4.5 hours (Smith *et al.*, 1983) and 11.2 hours(Ochs and Knüchel, 1984) in a three-compartment model and 2 hours in two-compartment model(Oyama,

1978). This discrepancy among reporters may be explained partly by the use of different model for the estimation of $t_{1/2\beta}$ (Echizen and Eichelbaum, 1986) or by differences in the final sampling time(McAllister et al., 1986). The differences of the terminal half-lives of diltiazem between dog and human can be explained by the different rate of hepatic metabolism. Diltiazem is largely cleared by hepatic metabolism (Rovel et al., 1980). The present study showed 2.5 L/kg/hr of hepatic clearance in six dogs, which was 2 or 3 times greater than that of report of Smith et al. (0.71 L/kg/hr) and Herman et al. (1.28 L/kg/hr) who studied in human, though the Vdss in our study (4.42 L/kg) was similar with the values (3.34 L/kg and 5.3 L/kg) of them. Generally, dogs have a greater hepatic drug clearance than humans (Goldstein et al., 1972).

Soward et al. (1986) suggested that the antianginal effect of diltiazem was due mainly to a reduced oxygen demand caused by a decrease in heart rate and a less pronounced fall in systolic blood pressure. Also it has been reported that hemodynamic and electrophysiological effects were well correlated to the plasma diltiazem concentration(Browne et al., 1983; Taeymans et al., 1982). Joyal et al. (1986) reported the blood pressure lowering effect was correlated to the plasma dilitiazem concentration, and the minimum effective plasma concentration was about 96 ng/ml. Similar to the report on human, in this study the blood pressure lowering effects of diltiazem became negligible within 90 minutes after starting the intravenous infusion, and the corresponding plasma levels were reached to less than 100 ng/ml.

The study of Smith et al. (1983) showed a 14% increase of P-R interval after a 10-minute infusion of 20 mg diltiazem in 13 patients, which was compared to the effect of verapamil with 25% prolongation of P-R interval found after only 10 mg dose over 2 minutes(Reiter et al., 1982). The negative dromotropic effect of diltiazem was apparent in a dose-dependent manner in this study. The P-R interval increased upto 27.7% in about 1.0 mg/kg , 34.25% in 1.43 mg/kg and 45.42% in a 1.85 mg/kg dose of diltiazem. The present study found counterclockwise hysteresis in the plasma diltiazem concentration vs. the P-R interval prolongation relationship(Fig. 4). This phenomenon is probably due to a delay in the transfer of diltiazem from the plasma to the effect site.

There were linear relationships between the P-R interval prolongation effect and the simulated effect site diltiazem concentration, in five out of six dogs in this study. In the Dog No. 6, in which a 1.85 mg/kg dose was actually administered, Emax model was best fitted to the data, and Emax for the P-R interval prolongation was 99 msec (55.2% of the control) and EC_{50} was 667 ng/ml. The mean peak effect site level simulated in the four dogs administered about 1.0 mg/kg does was 563.5 ng/ml, which was low in compariso to the EC_{50}. If observed drug concentrations are not sufficiently high relative to EC_{50}, the effect be comes proportional to the effect site concentration, and linear model will be best fitted to the effect data (Holford and Sheiner, 1981). For the estimation of Emax of P-R interval prolongation in these experimental dogs, at least 1.5 mg/kg does might be administered.

Active metabolites of diltiazem have been found in human, dog and rat. Among several metabolites, desacetyldiltiazem had a most potent action on vasodilation(40-50% of parent compound) and the second most potent one is N-monodemethyl diltiazem(Rovei et al., 1980; Yabana et al., 1985). In our study, however, these metabolites would not have greatly contributed to the cardiovascular action of the diltiazem because only 10-30% of desacetyl metabolite was produced from a single dose of the parent compound for 6-8 hours (Rovei et al., 1980). In multiple does, however, the cardiovascular effects of diltiazem would be affected by a active metabolites due to their accumulation in the body.

An understanding of the does-plasma concentration-effect site concentration-cardiovascular effects of dilitiazem would give a basic data for the optimum uses in controlling various cardiovascular disorders.

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= 국문초록 =

마취견에서 Diltiazem의 약동학 및 약력학 연구

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심맥관계 질환의 치료제로 이용되는 calcium channel 차단제인 diltiazem의 약동학 및 약력학적 효과를 동시 분석하고자 6마리의 잡견에 diltiazem HCl을 10분에 걸쳐 주입한후 6시간까지 경시적인 혈장농도 및 P-R interval, 혈압 및 심박수의 변동을 측정하였다. Diltiazem의 작용수용체부위 농도변화에 따른 심맥관계 약리작용의 상관관계를 분석하기 위해 약동학/약력학 동시 model을 사용하여 parameter들을 산출하였다. Diltiazem을 10분에 걸쳐 정맥 주입후 약 1 mg/kg 용량을 투여한 4마리의 개에서는 743.1 ± 224.6 ng/ml, 1.43 및 1.85 mg/kg 용량을 투여한 개에서는 각각 1151.5 및 1177.4 ng/ml의 최대혈장 농도치에 도달한 후 triexponential한 혈장 농도의 감소를 보였다. Diltiazem의 혈장반감기는($t_{1/2\beta}$)는 2.0 ± 0.5시간 이었으며 분포용적(Vdss)및 총 체내 청소율(Cl)은 각각 4.42 ± 0.87 L/kg 및 25.5 ± 6.6 L/hr이었다. P-R interval은 약 1.0 mg/kg, 1.43 mg/kg 및 1.85 mg/kg의 diltiazem 용량에서 각각 27.79 ± 12.48%, 34.25% 및 45.42% 까지의 연장효과를 나타내었으며 이완기 혈압은 각각 16.75 ± 8.26%, 19.69% 및 30.45%의 최대감소 효과를 보였다. P-R interval 대 biophase diltiazem 농도 상관관계는 5마리의 실험견에서는 직선적인 관계를 보였으나 1.85 mg/kg를 투여한 실험견에서는 hyperbolic한 관계를 보였다. Diltiazem의 P-R interval 연장효과로부터 산출된 평형속도상수(keo)는 0.46 ± 0.33 min⁻¹이었으며 5마리의 실험견에서 산출된 직선상관관계의 기울기 상수(α)는 0.063 ± 0.002이었다. Emax model을 사용한 1마리의 실험견에서 산출된 Emax는 99 msec, EC_{50}는 667 ng/ml이었다.

혈압 강하효과 대 biophase diltiazem 농도와의 관계는 6마리 모두 직선적이었으며 산출된 keo는 1 min⁻¹ 이상이었고 α는 0.069 ± 0.042이었다.