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Pharmacokinetics and Pharmacodynamics of Pimobendan-Pentoxifylline Liquid Mixture After Oral Administration in Dogs

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Abstract : Pimobendan is an inodilator used to treat canine heart failure, and pentoxifylline is reported to be beneficial for microcirculation and heart disease. The purpose of this study was to evaluate the pharmacokinetic and pharmacodynamic profiles of a novel pimobendan-pentoxifylline liquid mixture after oral administration to dogs. Eight healthy Beagle dogs were included in the study. The dogs were divided into the control group (orally administered water; n = 4) and experimental group (orally administered pimobendan-pentoxifylline liquid mixture [pimobendan 0.25 mg/kg, pentoxifylline 15 mg/kg]; n = 4). Plasma samples were obtained and echocardiographic indices were measured for 24 hours after administration. The concentrations of pimobendan and pentoxifylline were quantified by using a liquid chromatography-mass spectrometer (LC-MS). The elimination half-life ($T_{1/2}$) was 32.96 ± 9.80 mins for pimobendan and 29.49 ± 6.67 mins for pentoxifylline. The time to reach maximum concentration (T_{max}) were 52.50 ± 31.22 mins for pimobendan and 41.25 ± 18.87 mins for pentoxifylline. The maximum blood concentration (C_{max}) was 96.92 ± 75.64 ng/mL for pimobendan and 7074.07 ± 3261.1 ng/mL for pentoxifylline. Of the echocardiographic indices, fractional shortening (FS) and left ventricular internal diameter at end systole (LVIDs) were significantly altered at 1-3 hours after the administration of pimobendan-pentoxifylline liquid mixture. The pimobendan-pentoxifylline liquid mixture was well tolerated by the dogs, with no adverse effects observed during the study.

Key words **:** pimobendan, pentoxifylline, liquid mixture, dogs.

Introduction

The popularity of domestic companion animals has continued to increase; in parallel, the incidence of valvular heart disease in older dogs has also increased. Heart disease caused by valvular degeneration is particularly common in small-breed dogs, which are the most common type of dogs in Korea. Therefore, the development of novel drug components and formulations for the treatment of valvular heart disease has become more important.

One of the most widely used therapeutic agents for heart diseases, pimobendan, is a phosphodiesterase III inhibitor and a calcium sensitizer that has simultaneous inotropic and vasodilatory effects (6). In recent years, pimobendan has been used effectively for the treatment of canine congestive heart failure (1,5).

Pentoxifylline, a synthetic methylxanthine drug, is known to ameliorate peripheral vascular disease, ischemic injury, and heart failure through its hemorheologic and anti-inflammatory effects (8,11). In addition, pentoxifylline also has a protective effect on the coronary artery, which may be relevant to dogs with mitral valve insufficiency (11).

Therefore, a combination therapy with pimobendan and pentoxifylline is expected to exert synergistic effect on dogs with heart disease. In addition, the administration of these drugs, which are currently used in tablet formulation in our country, as a liquid formulation will allow the precise control of dosage in dogs with heart disease. This study was based on the experimental design of previous studies on pimobendan and pentoxifylline in dogs (2,7,10), and aimed to evaluate the pharmacokinetics and pharmacodynamics of a novel pimobendan-pentoxifylline liquid mixture after oral administration in healthy Beagle dogs.

Materials and Methods

Animals

Eight healthy intact male Beagle dogs (body weight, 10-12 kg) were analyzed in the study. The pre-experimental assessments, comprising physical examination, complete blood count, serum chemistry, and urinalysis, were conducted and all results were within normal range. All dogs were acclimatized to the same environment (constant temperature and humidity) for 1 week before the experiment. The dogs were fed twice a day with a specific product (Natural Balance LID Potato & Duck Grain Free, Natural Balance). This study was approved by the KBNP Institutional Animal Care and Use Committee (R0006046).

Experimental design

The experimental design of this study was determined after reference to the previous studies (7,10). The dogs were ran-

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domly divided into two groups: control and experimental groups, and received a single administration of the same dose of the drugs. Investigators involved in the drug administration were blinded to treatment information until the blood concentration data and the echocardiography results were obtained.

Experimental procedure

Before the experiment, all dogs were subjected to a physical examination, blood pressure measurement (petMAP^{TM}, Ramsey Medical), and echocardiography (EPIQ 7 Cardiology Ultrasound Machine, Philips) to confirm normal cardiac structure and the absence of cardiovascular disorders. The dogs were fasted for 12 hours prior to the drug administration, but given free access to water throughout the experimental period.

The control and experimental groups were orally administered 10 mL of water and pimobendan-pentoxifylline liquid mixture (pimobendan 0.25 mg/kg, pentoxifylline 15 mg/kg), respectively. Echocardiography was performed 30 minutes prior to administration, just before administration, and at 15 and 30 minutes, and 1, 1.5, 2, 3, 4, 8, 12, and 24 hours after administration. For the analysis of the drug concentrations, 5 mL of blood was collected from the jugular vein at 5, 10, 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 8, 12, and 24 hours after administration.

Echocardiography

The dogs were positioned in right lateral recumbency for echocardiography. A single investigator performed echocardiography in a consistent manner by using the EPIQ 7 Cardiology Ultrasound Machine (Philips, USA). The echocardiographic parameters determined were selected in reference to a previous study (10): left atrium; LA, aorta size; Ao, left atrium to aorta ratio; LA/Ao, interventricular septum diastole; IVSd, interventricular septum systole; IVSs, left ventricular posterior wall diastole; LVPWd, let ventricular posterior wall systole; LVPWs, fractional shortening; FS, aortic flow velocity; Ao vel, left ventricular ejection time; LVET.

Pharmacokinetic analysis

The pharmacokinetic analyses were performed at the Biomedical Science Research Institute, Hoseo University. The purpose of the study was to investigate the pharmacokinetics based on the effective plasma concentration of pimobendan and pentoxifylline in the active ingredient of the drug after oral administration of pimobendan-pentoxifylline liquid mixture to dogs. The plasma samples were collected at 5, 10, 15, 30, and 45 minutes and 1, 2, 3, 4, 8, 12, and 24 hours after oral administration, underwent a pre-analysis procedure, and were then analyzed by LC-MS/MS to determine the concentrations of pimobendan and pentoxifylline.

Sample preparation

After thawing the stored plasma at −70°C, 200 μL of the plasma was added to a 1.5 mL tube and 900 μL of acetonitrile was added. The mixture was vigorously shaken at 2,500 RPM for 10 minutes. After centrifugation at 15,000 *g* for 10 minutes, the supernatant was transferred to a 1.5 mL tube and concentrated under reduced pressure at 40°C to dryness. Subsequently, 200 μL of acetonitrile:distilled water (75:25, v/v) was added and redispersed for LC-MS/MS analysis (Fig 1).

Verification of analytical method and preparation of calibration sample

A QC sample was used to calculate the accuracy (recovery rate) and precision (coefficient of variation, CV) of a minimum of three measurements of each concentration. The analytical calibration curves were generated to quantify pimobendan and pentoxifylline in plasma. The limit of detection (LOD) was calculated as three times the signal to noise (S/N) ratio, and the limit of quantitation (LOQ) was calculated to be at least 10 times the S/N ratio.

LC-MS/MS analysis conditions

Mass spectrometry was performed by using an API 4000 MS/MS System (SCIEX, UA) and positive ions fragmented by ESI (electrospray Ionization) were detected by MS/MS mode. The mass spectrometer was optimized by flowing ace-

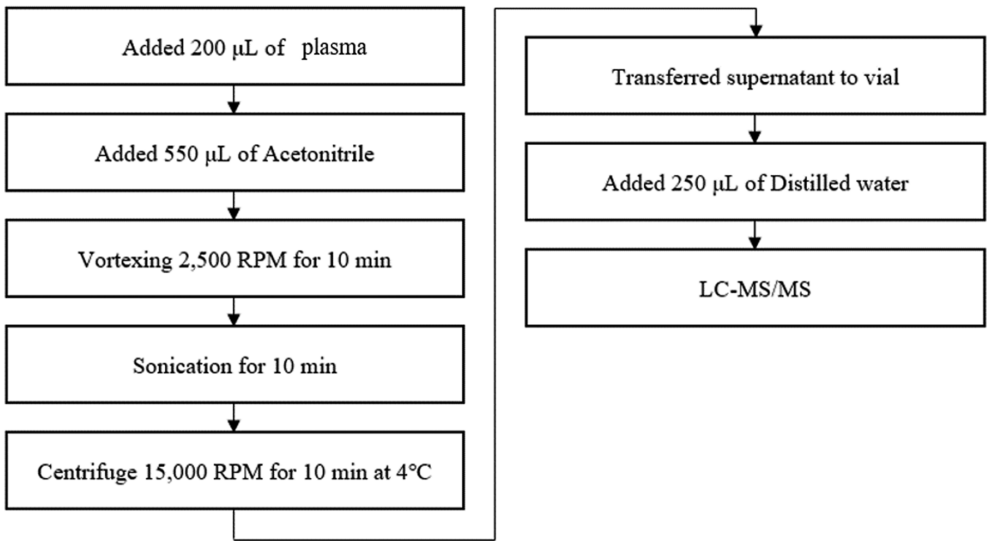

Fig 1. Sample preparation protocol for pimobendan and pentoxifylline analysis in dog plasma.

tonitrile mixed with 0.1% formic acid. The m/z of the product ions of pimobendan and pentoxifylline were 319.2 and 181.1, respectively.

Limit of detection (LOD) and limit of quantitation (LOQ)

A standard substance was added to the untreated dog plasma sample and the calibration curve was drawn for the pretreated sample. The LOD was three times the S/N (signal to noise) ratio for the standard deviation of the measured value. The LOQ was 10 times the S/N ratio. The LOD and LOQ of pimobendan were 0.2 ng/mL and 1 ng/mL, respectively. The LOD and LOQ of pentoxifylline were 10 ng/mL and 50 ng/mL, respectively.

Verification of analytic methods (accuracy and precision)

After the addition of each concentration to untreated plasma samples, the LC-MS/MS analysis showed excellent linearity with a correlation coefficient (r^2) of ≥ 0.99. From the pimobendan QC samples, the accuracy was within the range 82.80%-88.15%, with a coefficient of variation of 0.53%-0.90%. From the pentoxifylline QC samples, the average recovery rate was 81.42%-86.80%, with a coefficient of variation of 0.52%-1.26%.

In conclusion, the preliminary tests confirmed that the assay methods of both pimobendan and pentoxifylline were acceptable.

Pharmacodynamic analysis

The changes in the function and morphology of the heart after drug administration were determined from the changes in echocardiographic parameters over time. As the size of the heart is dependent on the weight of the dog, the measured value was corrected by weight, as described in a previous study (4). The analysis results were expressed as the mean and standard deviations, and the Mann-Whitney test method was used for the statistical analysis of the control and experimental groups. In this study, the presence of a statistically significant difference between before and after administration in each group, or between the control and experimental groups, was tested. The difference between the two values was defined as significant if the associated P-value was below 0.05. For statistical analysis, SPSS version 20 (SPSS, Inc., Chicago, IL, USA) was used.

Table 1. Pre-examination characteristics of 8 dogs included in this study

Characteristics	Dogs
Number	8
Gender	8 Males
Body weight (Kg), mean ± SD (Range)	10.8 ± 0.6
Heart rate (bpm), mean ± SD	132 ± 12
Respiratory rate (/min), mean ± SD	34 ± 9
Body temperature (°C), mean ± SD	38.6 ± 0.4
Hematologic evaluations	
WBC (× 10^3/μl)	10.5 ± 1.7
RBC (× 10^6/μl)	7.3 ± 0.4
Hb (gm/dl)	17.1 ± 1.1
PCV (%)	51.6 ± 3.3
PLT (× 10^3/μl)	290.8 ± 63.0

SD, standard deviation; CBC, complete blood count; WBC, white blood cell; RBC, red blood cell; Hb, haemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuacular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; PLT, platelets.

Results

Animals

The animals used in this study were eight Beagle dogs over 1 year of age; no dogs were found to have abnormal physical examination or laboratory tests results. The pre-examination characteristics of the eight dogs included in this study are shown in Table 1.

Pharmacokinetics

The pharmacokinetics of pimobendan were analyzed by LC-MS/MS. The time to maximum concentration (T_{max}) was 52.50 ± 31.22 minutes and the maximum concentration (C_{max}) was 96.92 ± 75.64 ng/mL. The area under curve ($AUC_{(inf)}$) was 5866.59 ± 3440.02 ng·min/mL and the half-life ($T_{1/2}$) was 32.96 ± 9.80 minutes.

In the pharmacokinetics of pentoxifylline, the time to maximum concentration (T_{max}) of pentoxifylline was 41.25 ± 18.87 minutes and the maximum concentration (C_{max}) was 7074.07 ± 3261.10 ng/mL. The area under curve ($AUC_{(inf)}$)

Table 2. Pharmacokinetic parameters of dogs (n = 4) administrated with pimobendan-pentoxifylline liquid mixture

Pharmacokinetic parameter	Unit	Analytes	
		Pimobendan	Pentoxifylline
Lambda z	min^{-1}	0.02 ± 0.01	0.02 ± 0.01
$AUC_{(last)}$	ng·min/mL	4,684.37 ± 3341.57	422,700.63 ± 89754.02
$AUC_{(inf)}$	ng·min/mL	5,866.59 ± 3440.02	426,161.81 ± 89212.45
C_{max}	ng/mL	96.92 ± 75.64	7,074.07 ± 3261.10
T_{max}	min	52.50 ± 31.22	41.25 ± 18.87
$T_{1/2}$	min	32.96 ± 9.80	29.49 ± 6.67
$CL_{(inf)}$/F	L/min/kg	0.00 ± 0.00	0.00 ± 0.00
$Vz_{(terminal)}$/F	L/kg	0.00 ± 0.00	0.00 ± 0.00

Lambda z, elimination rate constant; $AUC_{(last)}$, area under curve from time zero to 24 hours; $AUC_{(inf)}$, area under curve from time zero to infinity; T_{max}, time to maximum concentration; C_{max}, maximum concentration; $Vz_{(terminal)}$/F, apparent terminal volume of distribution.

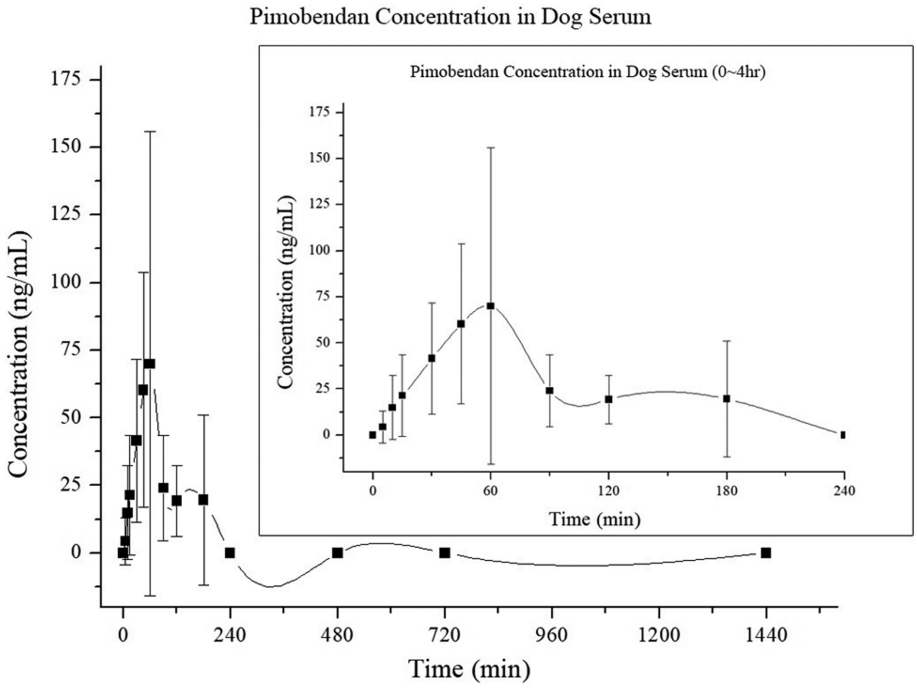

Fig 2. Time-course change graph of pimobendan concentration in plasma of dogs (n = 4) administrated with pimobendan-pentoxifylline liquid mixture, determined by LC-MS/MS depending on points of time.

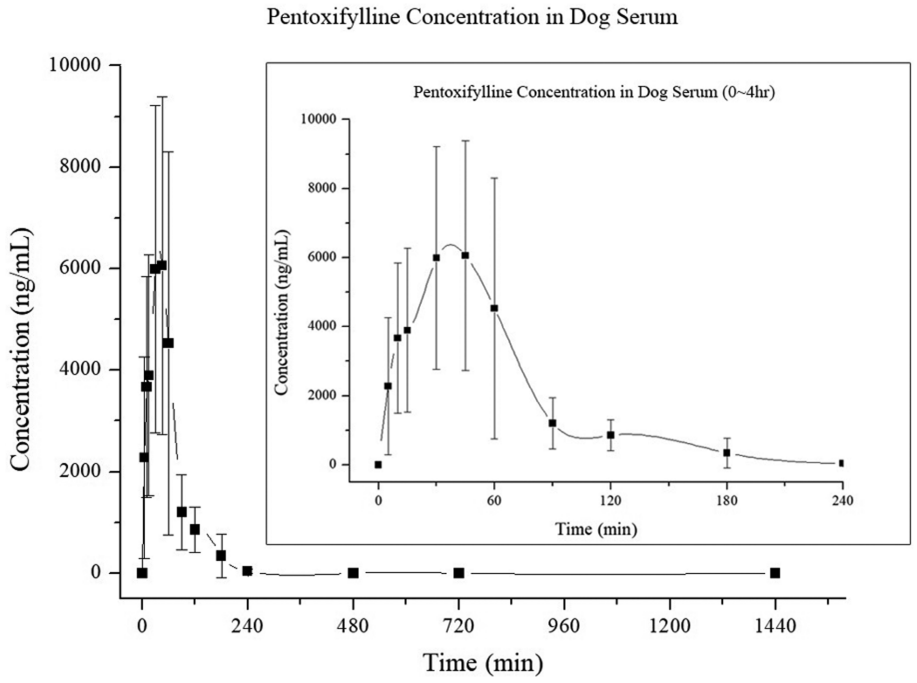

Fig 3. Time-course change graph of pentoxifylline concentration in plasma of dogs (n = 4) administrated with pimobendan-pentoxifylline liquid mixture, determined by LC-MS/MS depending on points of time.

was 426161.81 ± 89212.45 ng·min/mL and the half-life ($T_{1/2}$) was 29.49 ± 6.67 minutes.

The pharmacokinetic parameters of dogs administered with pimobendan-pentoxifylline liquid mixture are shown in Table 2.

The pimobendan and pentoxifylline concentration in the plasma of dogs administered the pimobendan-pentoxifylline liquid mixture are shown in Fig 2 and Fig 3, respectively.

Pharmacodynamics

There was no significant difference between the two groups in the baseline echocardiographic indices of the control and experimental groups before the drug administration (Table 3).

The following indices were significantly different from the baseline values in the experimental group administrated with the pimobendan-pentoxifylline liquid mixture: FS (between 30 minutes and 3 hours), LVIDs (between 30 minutes and 4

Table 3. Pre-examination echocardiographic indices of control group (n = 4) and experimental group (n = 4)

Parameter (units)	Control group	Experimental group
Ao Vel (m/s)	129.6 ± 28.8	91.2 ± 18.1
Ao* (cm)	1.5 ± 0.2	1.6 ± 0.2
FS (%)	39.9 ± 4.1	37.2 ± 3.1
HR (bpm)	138.0 ± 8.5	126.0 ± 13.9
IVSd* (cm)	0.7 ± 0.1	0.9 ± 0.1
IVSs* (cm)	0.8 ± 0.1	1.0 ± 0.1
LA* (cm)	1.8 ± 0.1	1.9 ± 0.1
LVET (ms)	200.0 ± 14.4	229.1 ± 16.2
LVIDd* (cm)	3.3 ± 0.2	3.2 ± 0.3
LVIDs* (cm)	2.0 ± 0.2	2.0 ± 0.1
LVPWd* (cm)	0.8 ± 0.1	0.8 ± 0.1
LVPWs* (cm)	1.1 ± 0.2	1.2 ± 0.1
PEP (ms)	24.3 ± 7.7	25.0 ± 1.2
MBP (mmHg)	96.4 ± 6.6	94.9 ± 3.5
DBP (mmHg)	78.8 ± 5.0	80.0 ± 1.8
SBP (mmHg)	131.8 ± 10.7	124.8 ± 8.7

Echocardiographic indices determined from a study in 2016 (10).
Ao Vel, aortic velocity; Ao, aortic diameter; FS, fractional shortening; HR, heart rate; IVSd, interventricular septum (diastole); IVSs, interventricular septum (systole); LA, left atrium; LVET, left ventricular ejection time; LVIDd, left ventricular internal diameter (diastole); LVIDs, left ventricular internal diameter (systole); LVPWd, left ventricular posterior wall (diastole); LVPWs, left ventricular posterior wall (systole); PEP, pre-ejection period; MBP, mean blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
All values were not significantly different between two groups ($P > 0.05$).
Values expressed as mean standard ± deviation.
*Indexed to body weight (4).

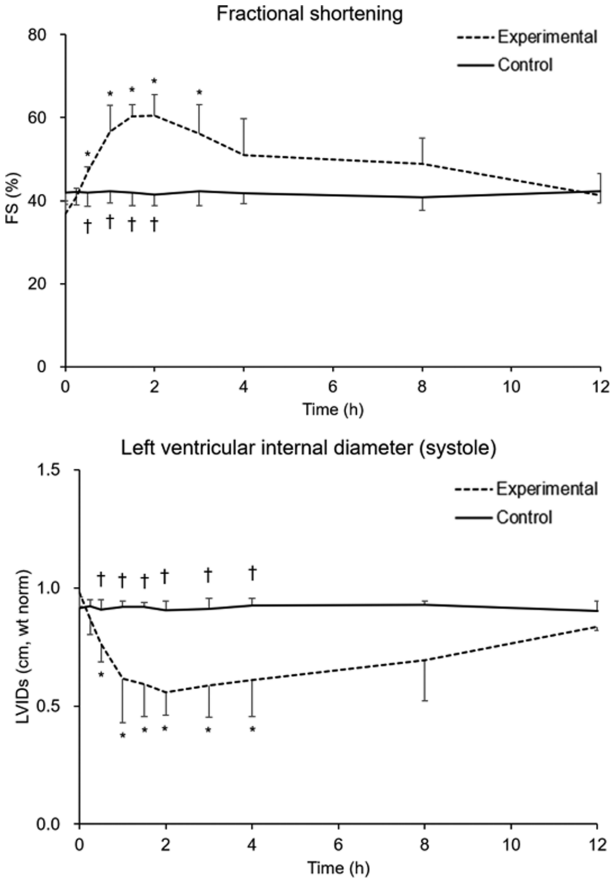

Fig 4. Echocardiographic indices (fractional shortening and left ventricular internal diameter systole) of control (n = 4) and experimental (n = 4) groups over time after administration of water and pimobendan-pentoxifylline liquid mixture, respectively. Measurement and expression of echocardiographic indices determined from the prior study (10). FS, fractional shortening; LVIDs, left ventricular internal diameter (systole); cm, wt norm, weight-normalized centimeters (4). *Significant difference ($P < 0.05$) from baseline (time 0) in the experimental group. There were no significant differences from baseline in the control group. †Significant difference ($P < 0.05$) between control and experimental groups. Mean and standard deviation are represented by point and bars, respectively.

hours) (Fig 4). Compared with the baseline values, FS was increased and LVIDs was decreased. The maximum effect of the drug appeared between 1 and 3 hours after administration, and a significant difference ($P < 0.05$) between the control and experimental group was observed from 30 minutes to 3 hours in FS and from 30 minutes to 4 hours in LVIDs.

Discussion

This study investigated the changes in healthy dogs after the administration of a novel pimobendan-pentoxifylline liquid mixture, and compared the pharmacokinetics and pharmacodynamics results with those of previous studies.

For Vetmedin® (Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany), which is the most commonly used pimobendan preparation in Korea, the maximum concentration following the oral administration of 0.25 mg/kg Vetmedin to healthy dogs, was 3.09 ± 0.76 μg/L in the previous study (3). For the pimobendan-pentoxifylline liquid mixture used in this study, the maximum concentration of pimobendan in plasma was 96.92 ± 75.64 ng/mL. This result was significantly higher than those of the Vetmedin tablets, and also higher than the maximum concentrations (39.4 ± 23.4 and 38.1 ± 18.3 μg/L, respectively) in the previous research in dogs orally administered pimobendan enantiomer as a liquid and capsule formulation (2). In addition, the maximum concentration of nonaqueous pimobendan solution in healthy dogs was 18.6 ng/mL in another study (10); thus, all experiments using liquid or capsule formulations of pimobendan yielded different maximum concentrations. As reported in the previous study (2), these differences in concentration may be caused by differences in sample types (plasma or whole blood), differences in experimental designs, such as analytic methods, and differences in the absolute bioavailability of each formulation.

The pimobendan-pentoxifylline liquid mixture in this study was considered to a have high bioavailability and absorption rate as it reached the highest maximum concentration in plasma. The time to maximum concentration was 2 hours for the Vetmedin tablet, 38.5 ± 15 minutes for the liquid formulation, and 53.9 ± 36.7 minutes for the capsule formulation in the pimobendan enantiomer experiment, and 1.1 hours for the nonaqueous pimobendan solution (2,7,10). In the present

study, the time to maximum concentration of pimobendan was 52.50 ± 31.22 minutes, which was considered rapid relative to the results of previous studies. The results of the present and previous studies indicated that the time to maximum concentration of the liquid formulation was shorter than that of the tablet or capsule formulation drug, and that the the pimobendan-pentoxifylline liquid mixture used in this study will also reach the maximum concentration within a short period of time, and to improve the emergency situation by acting effectively in dogs with congestive heart failure. In addition, the administration of pentoxifylline with pimobendan did not inhibit the absorption of pimobendan or cause specific interference, as confirmed by the maximum concentration and time to maximum concentration of pimobendan. The half-life was approximately 30 minutes for the Vetmedin tablet, 37.4 ± 8.5 minutes for the liquid formulation, and 37.3 ± 10.2 minutes for the capsule formulation in the pimobendan enantiomer experiment, and 0.9 hours for the nonaqueous pimobendan solution (2,7,10). In the present study, the half-life of the pimobendan-pentoxifylline liquid mixture was 32.96 ± 9.80 minutes, which was similar to those in previous studies. Thus, there was no specific differences in the processes of absorption, metabolism, and excretion of liquid pimobendan in dogs administered pentoxifylline.

In a previous study in which pentoxifylline tablets were orally administered to healthy dogs, the maximum concentration of pentoxifylline in plasma was 2.18 ± 0.34 μg/mL when administered with food, 1.95 ± 0.38 μg/mL when administered without food, and the time to maximum concentration was 47.5 ± 11.2 minutes and the half-life was 26.7 ± 5.0 minutes, respectively (7). In the present study, the maximum concentration of pentoxifylline in plasma was 7074.07 ± 3261.10 ng/mL, which was higher than that in the previous study. It is considered that, as shown by the concentration of pimobendan, the pimobendan-pentoxifylline liquid mixture has a high bioavailability and rapid absorption rate. The time to maximum concentration and the half-life of the pimobendan-pentoxifylline liquid mixture were 41.25 ± 18.87 minutes and 29.49 ± 6.67 minutes respectively, which were very similar to those of the previous study. Therefore, pentoxifylline was adequately absorbed and excreted without interference in the presence of co-administered pimobendan. The administration of pentoxifylline in the liquid formulation did not show a large difference from the administration of the tablet formulation, unlike pimobendan administration, in which the liquid formulation showed a shorter time to maximum concentration than the tablet formulation.

For the pharmacodynamic analysis of the pimobendan-pentoxifylline liquid mixture, the echocardiographic results of the present study were compared with those of a previous study, from which the echocardiographic parameters were referenced in this study (10). In the results of the previous study, the left ventricular FS and LVIDs were significantly changed from 2 hours and 1 hour, respectively, after the administration of the nonaqueous pimobendan solution and the maximally changed values of FS and LVIDs were approximately 45.1% and 0.74 cm at 3 hours, which were 34% and 26% different to the baseline value of 33.6% and 1.0 cm, respectively (10). In comparison, the FS and LVIDs were significantly different from 30 minutes after the administration of pimobendan-pentoxifylline liquid mixture and the maximally changed values of FS and LVIDs were 60.4% and 0.56 cm at 2 hours, which were 64% and 43% different to the baseline values of 36.9% and 0.99 cm, respectively. Thus, the pimobendan-pentoxifylline liquid mixture used in the present study resulted in a faster significant effect than the nonaqueous pimobendan solution used in the previous study, and also resulted in a greater change in the echocardiographic values. This rapid pharmacological action was consistent with the high resorption rate and fast time to maximum concentration identified in the pharmacokinetic properties. In addition, the higher rate of change compared with the existing pimobendan single agent is thought to be related to the high maximum concentration in plasma, and the concomitant administration of pentoxifylline, which can act as a phosphodiesterase inhibitor together with pimobendan, thereby reducing the afterload on the heart through relaxation of the blood vessels; this may have an additional effect on the increase in contraction force (9,11). Therefore, the pimobendan-pentoxifylline liquid mixture can be applied clinically with effective concentration control and rapid action for the treatment of patients with heart disease, and improvement of cardiac function is obtained through synergic effect of two drugs. It is expected that the quality of life in companion animals with valvular heart disease may be improved if further large-scale studies for the clinical application of the pimobendan-pentoxifylline liquid mixture are performed.

Conclusions

In this study, the pimobendan-pentoxifylline liquid mixture was orally administered to healthy dogs, and the maximum concentration was 96.92 ± 75.64 ng/mL for pimobendan and 7074.07 ± 3261.10 ng/mL for pentoxifylline, which were higher concentrations than those in previous studies. The time to maximum concentration was 52.50 ± 31.22 minutes for pimobendan and 41.25 ± 18.87 minutes for pentoxifylline, which are considered to be similar to or slightly faster than the results of previous studies. The half-life of the drug was 32.96 ± 9.80 minutes for pimobendan and 29.49 ± 6.67 minutes for pentoxifylline, and both pimobendan and pentoxifylline exhibited half-life similar to those of the prior studies. In the echocardiographic evaluation, the pimobendan-pentoxifylline liquid mixture used in this study started to show significant effect 30 minutes after administration in the echocardiographic parameters (FS, LVIDs) similar to those of the previous study, and the maximum effect of the drug was observed from 1 hour to 3 hours after administration. In this study, it was confirmed that the pimobendan-pentoxifylline liquid mixture was properly absorbed by dogs and effectively improved the cardiac function within a short period of time. These results may be helpful in directing further research and the clinical application of the pimobendan-pentoxifylline liquid mixture to dogs with heart diseases.

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