

Plasma Concentrations of an Angiotensin-Converting Enzyme Inhibitor, Benazepril, and Its Active Metabolite, Benazeprilat, after Repeated Administrations of Benazepril in Dogs with Experimental Kidney Impairment

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ABSTRACT. In order to examine the safety of an angiotensin-converting enzyme (ACE) inhibitor in dogs with impaired renal excretion route, benazepril was administered orally, and plasma concentrations of benazeprilat, the active metabolite of benazepril, were determined in dogs with renal mass reduction (1/4th kidney) created by right-side nephrectomy and ligation of branches of the left renal arteries. Five dogs were administered benazepril orally at a given dose (0.5 mg/kg body weight) and 4 other dogs received 20 times that dose (10 mg/kg body weight) once daily for 15 consecutive days before (intact kidney period) and after (1/4th kidney period) creation of kidney impairment. Six control dogs received surgical treatment, but no drug. After creating a 1/4th kidney, plasma urea nitrogen and creatinine concentrations increased to approximately 30 mg/dl and 2.0 mg/dl, respectively, and renal plasma flow and glomerular filtration rate decreased to 37% and 30% of pre-treatment values, respectively. However, these parameters did not change significantly during the 1/4th kidney period both in the 0.5 mg/kg and 10 mg/kg groups. In the 0.5 mg/kg group, plasma benazeprilat concentrations increased to approximately 20 ng/ml to 340 ng/ml 2 hr after each administration, and there were no significant differences between the plasma benazeprilat concentrations during the intact and 1/4th kidney periods. In the 10 mg/kg group, plasma benazeprilat concentrations varied in the individual dog, but did not increase with the days of administration, and were not significantly different on each administration day between the intact and 1/4th kidney periods in either dose group. The AUC_{S(0-24)} of plasma benazeprilat concentrations determined on the 15th administration day were not different between the intact and 1/4th kidney periods in dogs of either dose group. Plasma ACE activities decreased after drug administration in dogs of both groups. Benazepril seemed to have a high safety, and the adjustment of dosage regimen might not be needed in dogs with mild to moderate renal function impairment because the drug was excreted both from the kidneys and liver.—**KEY WORDS:** angiotensin-converting enzyme inhibitor, benazepril, canine, plasma concentration, renal impairment.

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Angiotensin-converting enzyme (ACE) inhibitors have been used widely as vasodilators for treatments of hypertension and heart disease in humans [14, 17, 23]. The drugs, such as captopril, lisinopril, enalapril, and benazepril, have also been used for treatment of congestive heart failure in dogs [1, 2, 5, 8]. Captopril and lisinopril act directly after absorption from intestines, and enalapril and benazepril do after conversions to active metabolites in the liver [10]. The ACE inhibitors represent an action to preserve renal function [12, 16]. Besides, their use is not recommended in human and animal patients with renal failure because the renal function impaired further [2, 13]. Most ACE inhibitors such as captopril, enalapril, and lisinopril, were excreted only from the kidney [10]. For drugs eliminated renally such as ACE inhibitors, any functional impairment of the kidney serves to delay drug elimination, and induces an increased risk of adverse reactions [18, 20]. Dogs with congestive heart failure have tended to suffer renal functional impairment [9], so that the use of an ACE inhibitor in these diseased dogs may induce some adverse reactions. Two ACE inhibitors are now in use for veterinary medicine; enalapril and benazepril [2]. These are both prodrugs, converted to active metabolites in the liver, and the former is excreted from the kidney [10, 18] and the later

from the liver and kidney [24]. In order to examine the safety of benazepril in dogs with impaired renal excretion route, the drug was administered orally at a clinically used dose of 0.5 mg/kg or a high dose of 10 mg/kg body weight once daily for 15 days in dogs with impaired renal function produced by renal mass reduction [22]. Clinical observation and laboratory examination were performed, and plasma concentrations of benazepril and benazeprilat, the active metabolite of benazepril, were determined.

MATERIALS AND METHODS

Fifteen mongrel dogs with normal clinical signs and plasma concentrations of urea nitrogen (UN) and creatinine (CRE), were used. Their body weight ranged from 7.8 to 11.1 kg. Thirteen dogs were male, and 2 were females, but there were no sex-related differences in the data. These dogs were all heartworm-free. Dogs were divided into 3 groups without intention. Five dogs were administered benazepril hydrochloride (Fortekor, Novartis Agro K.K., Tokyo) at 0.5 mg/kg body weight, and 4 dogs 10 mg/kg body weight once daily for 15 consecutive days (intact kidney period) (Fig. 1). The dogs were then treated surgically, and monitored carefully for 2 weeks as the

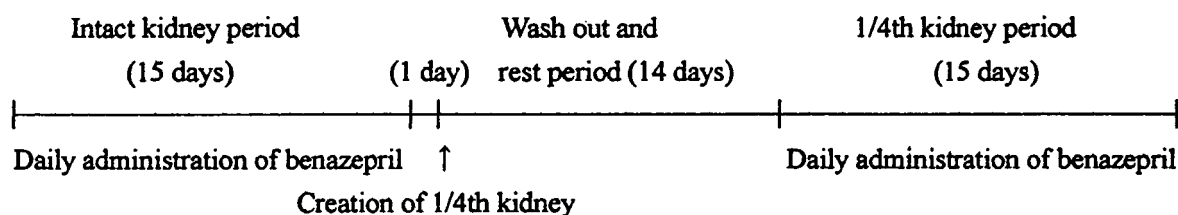


Fig. 1. Experiment schedule.

withdrawal and rest periods. They were then re-administered the same dose of benazepril once daily for 15 consecutive days (1/4th kidney period). Six control dogs received surgical treatment, but no drugs other than antibiotics. Dogs were housed individually, and provided a regular volume of a commercial dry dog food without salt restriction. Water was given freely, but the intake volume was recorded.

Dogs underwent laparotomy under general anesthesia with iv administration of diazepam (0.2 mg/kg body weight, Cercine, Takeda Chemical Industries, Osaka, Japan) and inhalation of isoflurane (Nissan Chemical Industries Ltd., Tokyo). Renal mass reduction was carried out by right-side nephrectomy and ligation of one of the branches of left renal arteries (i.e. 1/4th kidney) [22].

Clinical observations, and measurements of rectal temperature and heart rate were carried out daily. Heartworm infestation was denied by detections of circulating microfilariae (filter concentration method) and antigen (SNAP Heartworms, IDEXX Laboratories, Tokyo) and necropsy. Blood pressures were measured by the oscillometric method (BP-203NP, Nippon Colin Co., Ltd., Komaki, Japan). Plasma levels of biochemicals, such as UN, CRE, calcium, inorganic phosphorus, sodium, potassium, and chloride, were determined by the dry chemistry method (Dry-Chem 5500 V and 800 V, Fuji Photo-Film Co., Ltd., Tokyo) before the administration of the drug and on the 1st, 8th and 15th day of administration. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were determined from exogenous creatinine clearance and *para*-aminohippuric acid (PAH) clearance data, respectively, 2 hr after administration on the 1st, 8th, and 15th days. The urine protein concentration was determined by a colorimetric method [15]. Twenty-four hour urine protein excretion was calculated from urine protein concentration and 24-hr urine volume. Plasma ACE activity was determined before and 4 hr after administration of benazepril on the 1st, 8th and 15th days of administration by the Kasahara method [4].

Plasma benazeprilat concentrations were measured using a GC-MS with mass selective detection [6, 21]. Blood samples were collected before and 2 hr after oral administration of benazepril, which was the time for peak concentration of benazeprilat [6, 7] on the 1st to 5th, 8th, 10th, and 15th days of administration. On the 15th administration day, the plasma benazeprilat concentration was determined before and 2, 4, 8, 12 and 24 hr after

administration for calculation of the area under the curve (AUC_{0-24}). Differences in data among the 3 groups were tested using one-way ANOVA test, and differences between each administration day were done using Wilcoxon's matched pair test [3]. The study was conducted in manner consistent with the Guidelines for Animal Experimentation of Gifu University.

RESULTS

During the intact kidney period, 2 dogs in the 0.5 mg/kg group and 1 dog in the 10 mg/kg group showed a slight decrease in appetite, soft feces, and vomiting. The same clinical signs were observed in 1 or 2 dogs of either group during the 1/4th kidney period. However, their activities were normal. Body weight, rectal temperature, and heart rate did not change significantly. As shown in Table 1, blood pressures decreased slightly in dogs administered benazepril. However, low blood pressure (below 50 mm Hg) and clinical signs suggesting low blood pressure were not observed even in dogs of the 10 mg/kg group.

Table 2 shows results of laboratory renal function tests. During the intact kidney period, plasma UN and CRE concentrations of all dogs were within normal ranges even in dogs of the 10 mg/kg benazepril group. After creation of 1/4th kidney, those concentrations increased significantly ($P < 0.01$) in all groups, but did not change significantly during the 1/4th kidney period even with the high dose of benazepril. Plasma calcium, inorganic phosphorus, sodium, potassium, and chloride concentrations (data not shown) did not change significantly in both dose groups during the intact and 1/4th kidney periods. The RPF and GFR also did not change significantly in the two dose groups during the intact kidney period. After creation of 1/4th kidney, mean RPF and GFR values decreased to approximately 30% and 35%, respectively, compared with the values on the 1st day of administration during the intact kidney period. The RPF, and GFR did not change significantly during the 1/4th kidney period. Urine protein excretion increased after kidney removal, but decreased slightly, but not significantly in the 0.5 mg/kg group, and decreased significantly in the 10 mg/kg group during the 1/4th kidney period.

In the 0.5 mg/kg group (Table 3), pre-administration concentrations of plasma benazeprilat remained at low levels on each administration day, and did not differ significantly between administration days in the intact and 1/4th kidney periods. Plasma benazeprilat concentrations increased to

Table 1. Mean blood pressure in dogs of the control, 0.5 mg/kg and 10 mg/kg groups

Variable	Period	Administra- tion day	Control group		0.5 mg/kg group		10 mg/kg group	
			n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD
Mean blood pressure (mm of Hg)	Intact kidney	1	5	83 \pm 9	5	91 \pm 7	4	88 \pm 6
		8	5	73 \pm 8	5	84 \pm 18	4	78 \pm 8
		15	5	86 \pm 10	5	80 \pm 11	4	80 \pm 12
	1/4 kidney	1	5	84 \pm 6	5	83 \pm 13	4	86 \pm 12
		8	5	83 \pm 9	5	84 \pm 7	4	71 \pm 10
		15	5	83 \pm 6	5	82 \pm 18	4	78 \pm 12

SD: Standard deviation.

Table 2. Kidney function test results after administration of benazepril in dogs of the control, 0.5 mg/kg and 10 mg/kg groups

Variable	Period	Admin- istration day	Group					
			Control		0.5 mg/kg		10 mg/kg	
			n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD
Urea nitrogen (mg/dl)	Intact kidney	1	6	10.7 \pm 0.7	5	11.4 \pm 1.7	4	11.7 \pm 1.3
		8	4	11.5 \pm 2.3	5	9.6 \pm 2.1	4	9.7 \pm 1.1
		15	6	10.2 \pm 1.2	5	9.3 \pm 1.8	4	15.4 \pm 4.5
	1/4 kidney	1	6	31.5 \pm 5.3**	5	28.4 \pm 3.2**	4	32.3 \pm 7.5**
		8	5	36.8 \pm 3.5**	5	23.4 \pm 2.5**	4	32.8 \pm 10.0**
		15	6	32.1 \pm 3.8**	5	27.0 \pm 3.1**	4	33.5 \pm 6.3**
Creatinine (mg/dl)	Intact kidney	1	6	0.75 \pm 0.04	5	0.74 \pm 0.08	4	0.95 \pm 0.05
		8	4	0.78 \pm 0.06	5	0.60 \pm 0.09	4	0.75 \pm 0.06
		15	6	0.85 \pm 0.07	5	0.72 \pm 0.10	4	0.85 \pm 0.09
	1/4 kidney	1	6	2.08 \pm 0.23**	5	1.50 \pm 0.10**	4	1.83 \pm 0.17**
		8	5	1.84 \pm 0.23**	5	1.42 \pm 0.09**	4	1.75 \pm 0.12**
		15	6	2.07 \pm 0.31**	5	1.36 \pm 0.10**	4	1.65 \pm 0.13**
Renal plasma flow (ml/min/kg)	Intact kidney	1	5	8.49 \pm 0.75	5	6.88 \pm 1.24	4	8.29 \pm 1.17
		8	4	6.90 \pm 0.54	3	6.00 \pm 1.17	4	7.37 \pm 1.69
		15	5	6.48 \pm 0.72	5	6.13 \pm 0.85	4	8.59 \pm 1.27
	1/4 kidney	1	5	3.59 \pm 0.36**	5	1.85 \pm 0.19**	4	3.37 \pm 0.53**
		8	4	2.51 \pm 0.27**	5	1.89 \pm 0.21**	4	2.43 \pm 0.47**
		15	6	2.97 \pm 0.18**	5	2.04 \pm 0.12**	4	2.11 \pm 0.29**
Glomerular filtration ratio (ml/min/kg)	Intact kidney	1	6	3.62 \pm 0.16	5	3.21 \pm 0.46	4	2.90 \pm 0.49
		8	4	3.06 \pm 0.22	5	3.13 \pm 0.54	4	3.64 \pm 0.21
		15	6	2.75 \pm 0.10	5	3.11 \pm 0.63	4	3.62 \pm 0.83
	1/4 kidney	1	6	0.99 \pm 0.10**	5	0.81 \pm 0.08**	4	1.16 \pm 0.08**
		8	5	0.86 \pm 0.08**	5	0.89 \pm 0.13**	4	0.92 \pm 0.15**
		15	6	1.14 \pm 0.08**	5	0.89 \pm 0.08**	4	0.89 \pm 0.17**
Urine protein excretion (mg/24 hr)	Intact kidney	1	5	72 \pm 21	5	66 \pm 23	4	62 \pm 20
		8	4	84 \pm 20	5	75 \pm 36	4	90 \pm 38
		15	5	41 \pm 6	5	65 \pm 29	4	72 \pm 17
	1/4 kidney	1	5	171 \pm 42	5	160 \pm 47	4	329 \pm 93**
		8	4	112 \pm 23	4	172 \pm 71	4	132 \pm 30 ^{† †}
		15	5	118 \pm 37	5	91 \pm 22	4	135 \pm 30 ^{† †}

**: Significantly different from the value on the 1st administration day of intact kidney period (P<0.01).

† †: Significantly different from the value on the 1st administration day of 1/4 kidney period (P<0.01).

SD: Standard deviation.

approximately 20 ng/ml to 200 ng/ml 2 hr after administrations. One dog showed a high plasma benazeprilat concentration on the 2nd administration day

(330 ng/ml) of the intact kidney period, but the concentration decreased thereafter. There were no significant differences in mean concentrations 2 hr after administration between

Table 3. Plasma benazeprilat and benazepril concentrations before and 2 hr after administration of benazepril in dogs of the 0.5 mg/kg group

Phase	Admin- istration day	No. of dogs	Benazeprilat concentration (ng/ml)		P	Benazepril concentration (ng/ml)		P
			Intact kidney period	1/4 kidney period		Intact kidney period	1/4 kidney period	
			Mean \pm SEM	Mean \pm SEM		Mean \pm SEM	Mean \pm SEM	
Before administration (24 hr after adminis- tration)	1	5	1.1 \pm 1.1	0.3 \pm 0.3	NS	0 \pm 0	0 \pm 0	NS
	2	5	8.7 \pm 5.3	2.2 \pm 1.4	NS	0.3 \pm 0.3	0 \pm 0	NS
	3	5	4.8 \pm 0.9	3.6 \pm 2.2	NS	0 \pm 0	0.3 \pm 0.3	NS
	4	5	13.6 \pm 8.3	5.6 \pm 3.4	NS	0 \pm 0	0.4 \pm 0.4	NS
	5	5	3.8 \pm 1.7	4.0 \pm 2.5	NS	0 \pm 0	0.2 \pm 0.2	NS
	8	5	4.8 \pm 2.6	2.9 \pm 1.2	NS	3.7 \pm 3.7	0 \pm 0	NS
	10	5	8.3 \pm 3.9	1.9 \pm 1.9	NS	0.3 \pm 0.3	0 \pm 0	NS
2 hr after administration	15	4	1.3 \pm 1.3	3.1 \pm 1.3	NS	0 \pm 0	0 \pm 0	NS
	1	5	34.4 \pm 12.6	44.3 \pm 11.5	NS	9.4 \pm 6.5	3.8 \pm 3.8	NS
	2	4	118.7 \pm 71.1	96.0 \pm 28.7	NS	16.1 \pm 9.0	22.5 \pm 18.6	NS
	3	5	62.2 \pm 7.3	72.5 \pm 19.1	NS	4.8 \pm 2.4	14.9 \pm 12.7	NS
	4	5	72.8 \pm 10.9	91.8 \pm 29.3	NS	6.0 \pm 3.0	1.7 \pm 1.1	NS
	5	5	58.6 \pm 14.7	84.6 \pm 14.3	NS	1.1 \pm 1.1	3.1 \pm 0.9	NS
	8	5	91.9 \pm 34.6	66.4 \pm 16.5	NS	3.0 \pm 1.3	0.2 \pm 0.2	NS
AUC ₍₀₋₂₄₎	10	3	82.9 \pm 77.4	78.6 \pm 16.9	NS	1.3 \pm 0.7	0 \pm 0	NS
	15	4	89.3 \pm 40.8	79.2 \pm 13.7	NS	3.6 \pm 2.9	6.4 \pm 4.0	NS
			635 \pm 355	433 \pm 96	NS	7.3 \pm 5.7	12.9 \pm 8.1	NS

SEM: Standard error of mean.

P: Probability of significant difference between the values before and after kidney removal.

AUC: Area under the curve of plasma benazeprilat concentrations on the 15th administration day.

It is presented as ng.hr/ml.

Before administration: Before administration equals to 24 hr after administration from the 2nd day of administration.

the intact and 1/4th kidney periods. Moreover, plasma benazeprilat concentrations did not increase either in the intact or 1/4th kidney periods. Plasma benazepril concentrations were lower even 2 hr after administration in dogs of the 0.5 mg/kg group. There were no significant differences between the plasma benazepril concentrations during the intact and 1/4th kidney periods. The AUCs calculated from the plasma concentrations on the 15th administration day were not different between the intact and 1/4th kidney period.

In the 10 mg/kg group (Table 4), plasma benazeprilat concentrations before administration were considerably higher than those in the 0.5 mg/kg group. Concentrations during the 1/4th kidney period varied with individual dog, but mean concentrations were not significantly different between administration days during the intact and 1/4th kidney periods. Plasma benazeprilat concentrations 2 hr after administration showed considerably higher levels (above 1,000 ng/ml) in 2 dogs during 1/4th kidney period, but reduced on the 15th administration day, and mean concentrations on each administration day was not significantly different between the intact and 1/4th kidney periods. Plasma benazepril concentrations were lower than plasma benazeprilat concentrations also in the 10 mg/kg group, as well as in the 0.5 mg/kg group. Plasma benazepril concentrations varied with the individual dog, and did not increase with administration days. The AUC_{S(0-24)} of plasma benazeprilat and benazepril concentrations determined on

the 15th administration day were not different between the intact and 1/4th kidney periods also in dogs of the 10 mg/kg group.

Plasma ACE activities (Table 5) did not change significantly in the control group through the experiment. In the 0.5 mg/kg group, plasma ACE activities decreased gradually. Plasma ACE activities were below detectable levels (<1 IU/l) 4 hr after administration on the 8th and 15th day of the intact and 1/4th kidney periods, respectively. In the 10 mg/kg group, plasma ACE activities decreased markedly from 4 hr after administration on the 1st day of administration, and remained low both during the intact and 1/4th kidney periods.

DISCUSSION

Renal function in 1/4th kidney model dogs used in the present study may be different from naturally acquired renal impairment in the strict sense, because of differences in pathophysiology. However, the kidney function expressed as decreases in RPF and GFR may be common to the 1/4th kidney model and naturally occurring renal failure. After renal mass reduction, RPF and GFR decreased to 30 and 35% of the pre-surgical treatment levels, respectively, and plasma UN and CRE concentrations increased to approximately 30 mg/dl and 2.0 mg/dl, respectively. The functional impairment in the 1/4th kidney would be considered mild to moderate grade. Moreover, the

Table 4. Plasma benazeprilat and benazepril concentrations before and 2 hr after administration of benazepril in dogs of the 10 mg/kg group

Phase	Admin- istration day	No. of dogs	Benazeprilat concentration (ng/ml)			Benazepril concentration (ng/ml)		
			Intact kidney period	1/4 kidney period	P	Intact kidney period	1/4 kidney period	P
			Mean \pm SEM	Mean \pm SEM		Mean \pm SEM	Mean \pm SEM	
Before administration (24 hr after administration)	1	4	3 \pm 1	1 \pm 1	NS	1.7 \pm 1.8	0 \pm 0	NS
	2	4	59 \pm 10	199 \pm 65	NS	2.7 \pm 1.9	135 \pm 131	NS
	3	3	114 \pm 28	141 \pm 65	NS	2.4 \pm 1.0	14.0 \pm 7.3	NS
	4	3	93 \pm 25	306 \pm 66	NS	0.3 \pm 0.3	6.4 \pm 3.3	NS
	5	4	64 \pm 28	131 \pm 15	NS	1.9 \pm 1.5	11.4 \pm 6.1	NS
	8	4	97 \pm 29	208 \pm 35	NS	4.5 \pm 3.2	15.8 \pm 12.0	NS
	10	3	69 \pm 11	217 \pm 82	NS	2.6 \pm 2.6	21.7 \pm 8.4	NS
	15	4	98 \pm 14	213 \pm 59	NS	1.0 \pm 1.0	6.0 \pm 4.0	NS
2 hr after administration	1	4	1,439 \pm 157	2,290 \pm 1,124	NS	115 \pm 76	250 \pm 153	NS
	2	4	1,614 \pm 87	3,363 \pm 1,670	NS	86 \pm 19	506 \pm 262	NS
	3	4	1,579 \pm 394	2,884 \pm 761	NS	504 \pm 432	548 \pm 416	NS
	4	4	1,897 \pm 337	2,212 \pm 476	NS	210 \pm 75	373 \pm 239	NS
	5	4	2,149 \pm 459	3,160 \pm 748	NS	214 \pm 149	639 \pm 447	NS
	8	3	1,679 \pm 356	5,193 \pm 1,947	NS	109 \pm 49	888 \pm 357	NS
	10	4	2,126 \pm 322	4,951 \pm 1,021	NS	73 \pm 29	367 \pm 176	NS
	15	4	2,872 \pm 354	2,935 \pm 383	NS	105 \pm 56	545 \pm 210	NS
AUC ₍₀₋₂₄₎	15	4	10,969 \pm 2,011	15,758 \pm 4,732	NS	300 \pm 138	1,281 \pm 583	NS

SEM: Standard error of mean.

P: Probability of significant difference between the values before and after kidney removal.

AUC: Area under the curve of plasma benazeprilat concentrations on the 15th administration day.

It is presented as ng.hr/ml.

Before administration: Before administration equals to 24 hr after administration from the 2nd day of administration.

Table 5. Plasma ACE activities before and after administration of benazepril in dogs of the control, 0.5 mg/kg and 10 mg/kg groups

Variable	Period	Adminis- tration day	Sampling time		Control	0.5 mg/kg		10 mg/kg	
					Mean \pm SD	Mean \pm SD		Mean \pm SD	
ACE activity (IU/l)	Intact kidney	1	Before administration	5	5.1 \pm 0.4	5	3.9 \pm 0.4	4	3.3 \pm 1.2
			2 hr after administration	5	4.9 \pm 0.5	5	1.5 \pm 0.5	4	<1
		8	Before administration	5	4.1 \pm 0.8	5	3.5 \pm 0.4	4	0.6 \pm 0.1
			2 hr after administration	5	4.7 \pm 0.4	5	<1	4	<1
		15	Before administration	5	4.7 \pm 0.4	5	1.7 \pm 0.5	4	0.8 \pm 0.2
			2 hr after administration	5	4.9 \pm 0.7	5	<1	4	<1
	1/4 kidney	1	Before administration	5	3.8 \pm 0.8	5	4.1 \pm 0.7	4	4.1 \pm 1.3
			2 hr after administration	5	4.0 \pm 0.5	5	1.3 \pm 0.5	4	<1
		8	Before administration	5	4.5 \pm 0.7	5	2.4 \pm 0.9	4	<1
			2 hr after administration	5	4.6 \pm 0.7	5	<1	4	<1
		15	Before administration	5	5.2 \pm 0.8	5	1.7 \pm 0.8	4	<1
			2 hr after administration	5	5.2 \pm 1.0	5	<1	4	<1

Before administration on the 8th and 15th days equals to 24 hr after administration on the 7th and 14th days, respectively.

SD: Standard deviation. The value <1 calculated as 0.5 IU/l.

absorption of benazepril from the intestine and liver functions converting the benazepril to benazeprilat were normal in this dog model, because of low plasma benazepril concentrations and clinically meaning plasma benazeprilat concentrations in dogs of the 0.5 mg/kg group.

A few dogs showed a slight decrease in appetite, soft feces, and vomiting. However, their activities were normal. These signs were also observed in no drug-treatment dogs,

and incidences were not dose-dependent. Therefore, these symptoms might be not related with administrations of benazepril. Not only in dogs with intact kidneys but also in those with impaired kidneys, either dose of benazepril for 15 consecutive days failed to induce deterioration of clinical signs and renal function. The clinical and laboratory data obtained from the both dose groups suggest that benazepril can be used safely in dogs with a rather severe renal

dysfunction, when take a dose (10 mg/kg) used in the present study into consideration. Because of the drug accumulation in animals having an impaired kidney, the risk of adverse effects may increase in the administration of a drug eliminated from the kidneys [11]. The fact in the present study that the plasma concentrations of benazeprilat were not significantly different between the dogs with intact and impaired kidneys given 0.5 mg/kg of benazepril indicated that there were no accumulations of the drug also in dogs with impaired renal function. Besides, higher plasma benazeprilat concentrations were detected transiently in a few dogs of the 10 mg/kg group during the 1/4th kidney period. These might reflect a large amount of benazepril absorption from the normal intestine and conversion to benazeprilat in the functionally intact liver, and/or a decrease in drug excretion route because of renal mass reduction. However, the increased plasma benazeprilat concentrations decreased until the 15th administration day in spite of daily administration. These data suggested that benazeprilat did not accumulate even following administration of the 20-fold clinical dose of benazepril for 15 consecutive days. Almost the same AUCs determined before and after 1/4th kidney creation on the 15th administration day might corroborate why benazeprilat did not accumulate in dogs with impaired renal function. Generally, drugs which are excreted from the kidney need dosage adjustment in patient dogs with impaired renal function, because of the drug accumulation [11, 19]. In the present study, however, no abnormal laboratory test results nor accumulation of benazeprilat were observed, even in dogs administered the 20-fold higher dose rate than conventional clinical doses for 15 consecutive days. Therefore, it seemed that the adjustment of the benazepril dosage regimen might not be necessary, at least in dogs with mild to moderate renal failure, because benazeprilat is eliminated directly both from the renal route and biliary route [24].

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