Effects of Benidipine on Renal Function in Anesthetized Spontaneously Hypertensive Rats

Hideaki Kusaka, Hiroko Nomura and Akira Karasawa

Department of Pharmacology, Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411, Japan

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ABSTRACT—Effects of benidipine on urine volume, excretion of electrolytes and renal hemodynamics were investigated in anesthetized spontaneously hypertensive rats (SHR). Benidipine at 3 and 10 μg/kg (i.v.) significantly increased urine volume, sodium (Na) and potassium (K) excretion with no change of creatinine clearance (C_{CRE}). The increase in K excretion was relatively slight when compared with that in Na excretion. In another series of experiments, the tubular sites of action of benidipine were determined by the lithium clearance (C_{Li}) technique and the stop-flow method. Benidipine at 3 μg/kg (i.v.) increased C_{Li}, decreased creatinine concentration and increased Na concentration in the stop-flow urine from the distal nephron. These results suggest that benidipine produces diuresis and natriuresis by the inhibition of water and Na reabsorption at both the proximal tubule and the distal nephron. Benidipine increased *p*-aminohippuric acid clearance, but not C_{CRE}, at doses of 3 and 10 μg/kg (i.v.), suggesting that benidipine dilates the glomerular efferent arteriole as well as the afferent arteriole. It is, therefore, expected that benidipine does not cause intraglomerular hypertension and has a beneficial effect in progressive renal disease.

Keywords: Calcium antagonist, Diuretic effect, Renal hemodynamics

Benidipine is a 1,4-dihydropyridine calcium antagonist (1) that has long-lasting antihypertensive and antianginal activities (2, 3). Additionally, benidipine shows diuretic and natriuretic effects in saline-loaded normotensive rats (4).

In general, calcium antagonists have diuretic and natriuretic properties (5-9). However, the mechanism for the diuretic and natriuretic effects of calcium antagonists is complicated as they influence renal blood flow (RBF), glomerular filtration rate (GFR), glomerular mesangium and renal tubular function. Marre et al. (5) reported that in an isolated rat kidney preparation, nifedipine produced significant diuresis and natriuresis with no change in the GFR. Nicardipine infused intrarenally into hydropenic or hydrated dogs evoked diuretic and natriuretic actions by inhibiting the reabsorption of water and sodium (Na) at the proximal tubules with an increase in GFR and RBF (6). In anesthetized spontaneously hypertensive rats (SHR), amlodipine produced diuresis and natriuresis by inhibition of the reabsorption of water and Na at the loop of Henle, distal tubule and collecting ducts (7). On the other hand, the diuretic and natriuretic dose of felodipine had no effect on GFR; and in a micropuncture experiment, this drug inhibited the reabsorption of water and Na at the distal tubule and the collecting duct, but not at the proximal tubule or the loop of Henle (8). Thus, the mechanism for the diuretic and natriuretic effect of the calcium antagonist is still controversial. The mechanism of action may be different among the various calcium antagonists.

In the present study, we investigated the effects of benidipine on GFR, renal plasma flow, urine volume and excretions of electrolytes in anesthetized SHR by a clearance study. Additionally, the tubular sites of action were investigated by a lithium clearance study and the stop-flow experiment.

MATERIALS AND METHODS

Experimental animals

Male spontaneously hypertensive rats (SHR; Hoshino Experimental Animals, Saitama) weighing 325-450 g were used in the present study. The animals were kept at 22℃ and in a 12-hr light dark cycle. They had free access to tap water and commercial chow prior to the experiment.

Drugs

Benidipine (hydrochloride, KW-3049) was synthesized in our laboratories. Creatinine (CRE) and *p*-aminohippuric acid (PAH) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka) and Sigma Chemical Co. (St. Louis, MO, USA), respectively. All other chemicals and solvents were used in their analytical pure form. Benidipine was dissolved in saline containing Tween 80 (0.13 mg/ml) (vehicle).

Clearance study

SHR were divided into the 4 groups, consisting of 7 SHR in each group; i.e., one group treated with vehicle (control) and the 3 groups treated with benidipine (1, 3 and 10 μg/kg). SHR were anesthetized with pentobarbital Na (50 mg/kg, i.p.). The left carotid artery, right femoral vein and the urinary bladder were cannulated for blood collection, influsion and urine collection, respectively. Saline containing CRE (0.01 mg/ml), PAH (5 mg/ml) and pentobarbital Na (2 mg/ml) was infused with a constant flow infusion pump (Pump 22; Harvard Apparatus, Inc., South Natick, MA, USA) at a rate of 3 ml/rat/hr. After equilibration for 90 min, the vehicle was intravenously administered to all SHR, and urine was collected during a 1-hr control period. After the control period, benidipine (1, 3 or 10 μg/kg) was intravenously administered to SHR, and urine was collected during a 1-hr clearance period. In the control group, the vehicle was intravenously administered again. About 0.7 ml of blood was collected into a microtube containing heparin at the midpoint of each urine collection period, and plasma was separated immediately. Benidipine and the vehicle were intravenously administered to SHR at a volume 0.5 ml/kg. Concentrations of CRE in plasma and urine were determined by an autoanalyzer (AU510; Olympus, Tokyo). Concentrations of Na and potassium (K) in the plasma and urine were determined by flame photometry (775-A; Hitachi Ltd., Tokyo). Concentrations of PAH in the plasma and urine were determined by the Bratton-Marshall method (10). Standard formulas were used to calculate CRE clearance (C_{CRE}), as an index of GFR and to calculate PAH clearance (C_{PAH}), as an index of RPF. Reabsorption rates of water, Na and K at tubular sites were calculated from the following formulas:

$$\text{Reabsorption rate of water (\%)} = \frac{C_{CRE}\,(\text{ml/kg/hr}) - \text{Urine volume (ml/kg/hr)}}{C_{CRE}\,(\text{ml/kg/hr})} \times 100$$

$$\text{Reabsorption rate of Na (\%)} = \frac{C_{CRE}\,(\text{ml/kg/hr}) \times \text{Plasma Na}\,(\mu\text{Eq/ml}) - \text{Na excretion}\,(\mu\text{Eq/kg/hr})}{C_{CRE}\,(\text{ml/kg/hr}) \times \text{Plasma Na}\,(\mu\text{Eq/ml})} \times 100$$

$$\text{Reabsorption rate of K (\%)} = \frac{C_{CRE}\,(\text{ml/kg/hr}) \times \text{Plasma K}\,(\mu\text{Eq/ml}) - \text{K excretion}\,(\mu\text{Eq/kg/hr})}{C_{CRE}\,(\text{ml/kg/hr}) \times \text{Plasma K}\,(\mu\text{Eq/ml})} \times 100$$

Lithium clearance (C_{Li}) study

C_{Li} study was performed according to the previous methods (9, 11). SHR were divided into the 2 groups, consisting of 5 SHR in each group; i.e., one group treated with vehicle (control) and the other group treated with benidipine (3 μg/kg). SHR were anesthetized with pentobarbital Na (50 mg/kg, i.p.). The left carotid artery, right femoral vein and the urinary bladder were cannulated for blood cllection, infusion and urine collection, respectively. Saline containing lithium (Li) carbonate (0.28 mg/ml), CRE (0.0046 mg/ml) and pentobarbital Na (3.7 mg/ml) was infused with the constant flow infusion pump at rate of 2.16 ml/rat/hr. After equilibration for 2 hr, urine and plasma were collected according to the same procedure as described before. The dose of benidipine examined was 3 μg/kg (i.v.), which induced diuresis and natriuresis in the preceding clearance study. Concentrations of CRE, Na, K in plasma and urine were determined as previously described. The Li concentrations in the plasma and urine were determined by flame photometry. The standard formulas were used to calculate C_{CRE} and C_{Li}.

Stop-flow experiments

Stop-flow experiments were performed, using 4 SHR in each group, according to the previous method (11). SHR were anesthetized with pentobarbital Na (50 mg/kg, i.p.). After ligating the vascular pedicle of the right kidney, polyethylene catheters were cannulated into the left carotid artery, right femoral vein and the left ureter for blood collection, infusion and urine collection, respectively. After the surgery was completed, saline containing 0.15 g/ml mannitol and 0.005 mg/ml CRE was infused with the constant flow infusion pump at a rate of 30 ml/kg/hr. To maintain the condition of anesthesia, pentobarbital Na at 25 mg/kg/hr was continuously infused into the tail vein. After equilibration for 30 min, the vehicle was administered to all SHR. Five minutes after the administration of vehicle, the left ureter was clamped for 10 min. Upon release of occlusion, 15 samples of 3 drops of urine (about 40 μl) were collected into microtubes. About 0.7 ml of blood was collected immediately into a microtube containing heparin after the urine collection, and the plasma was separated. After recovery, the same procedure was repeated 5 min after the administration of benidipine (3 μg/kg, i.v.) to estimate the influence of benidipine on the stop-flow pattern. Thus, the left ureter was clamped two times in each animal. Benidipine and the vehicle were

intravenously administered to SHR at a volume of 0.5 ml/kg. Concentrations of CRE and Na in the plasma and urine were determined. The following parameters were calculated: $[U/P]_{CRE}$=[urinary CRE concentration] /[plasma CRE concentration], which estimates the reabsorption of water at the distal nephron (12, 13); $[U/P]_{Na}/[U/P]_{CRE}$=[urinary Na concentration]/[plasma Na concentration]/$[U/P]_{CRE}$, which estimates the reabsorption of Na at the distal nephron (12, 13).

Statistical analyses

Data are presented as means±S.E. Statistical significance was estimated by the paired *t*-test. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Clearance study

The results of the clearance study are shown in Table 1. No significant difference was found in the basal value of each parameter among all the groups. Benidipine at doses of 3 and 10 μg/kg (i.v.) produced marked increases in urine volume and Na excretion. Benidipine also produced a slight but significant increase in K excretion. However, the increase in K excretion was relatively slight when compared with that in Na excretion. Benidipine at 3 and 10 μg/kg (i.v.) caused a significant increase in C_{PAH} with little increase in C_{CRE}, resulting in a significant decrease of the filtration fraction (FF). Benidipine at these doses, which exhibited diuretic and natriuretic effects, significantly inhibited the reabsorption of water, Na and K at the tubular site.

C_{Li} study

Table 2 shows the results of the C_{Li} study. In the present study, the Li concentration in plasma was 0.35 to 0.72 mEq/l. No significant difference was found in the basal value of each parameter between the control and the benidipine (3 μg/kg, i.v.)-treated group. Benidipine at 3 μg/kg (i.v.) significantly increased the urine volume and Na excretion without any change of C_{CRE}, as was the case with the clearance study. Benidipine at this dose significantly increased C_{Li}.

Stop-flow experiments

Figure 1 shows $[U/P]_{CRE}$ and $[U/P]_{Na}/[U/P]_{CRE}$ before and after the administration of benidipine. In the preliminary experiment, in which CRE (50 mg/kg, i.v.) was administered just before releasing the clamp, the highest concentration of CRE in the urine was observed in fraction No. 15. The highest concentration of CRE indicates roughly the entry of new glomerular filtrate. In the control experiment, when the vehicle was repeatedly administered, sequential stop-flow patterns in all animals were found to be reproducible (data not shown). Benidipine (3 μ/kg, i.v.) significantly decreased $[U/P]_{CRE}$ and increased $[U/P]_{Na}/[U/P]_{CRE}$ in specimens from the distal nephron.

Table 1. Effects of benidipine on renal function in anesthetized SHR

	Control		Benidipine, 1 μg/kg (i.v.)		Benidipine, 3 μg/kg (i.v.)		Benidipine, 10 μg/kg (i.v.)	
	before	after	before	after	before	after	before	after
Urine volume (ml/kg/hr)	2.13 ±0.53	2.30 ±0.51	2.08 ±0.53	2.48 ±0.50	1.98 ±0.31	3.93*** ±0.50	2.30 ±0.63	5.45** ±0.94
Na excretion (μEq/kg/hr)	380.9 ±60.1	385.2 ±80.5	362.0 ±57.4	454.6 ±88.4	377.2 ±93.4	865.9*** ±142.5	424.8 ±63.1	1185.5** ±175.3
K excretion (μEq/kg/hr)	233.9 ±10.9	243.1 ±11.3	221.0 ±13.2	249.1 ±18.2	228.8 ±16.0	291.8* ±13.6	245.0 ±5.6	322.7*** ±14.2
C_{CRE} (ml/kg/hr)	129.1 ±5.8	139.4 ±4.9	131.9 ±7.0	131.2 ±7.8	126.5 ±6.7	142.4 ±7.5	130.3 ±4.4	144.4 ±8.7
C_{PAH} (ml/kg/hr)	873.5 ±72.1	1897.7 ±48.1	793.6 ±41.4	879.6 ±40.6	904.8 ±68.7	1493.1*** ±86.0	845.4 ±44.3	1909.9*** ±176.2
FF	0.152 ±0.011	0.159 ±0.012	0.167 ±0.008	0.150** ±0.009	0.142 ±0.006	0.098** ±0.008	0.155 ±0.005	0.078*** ±0.006
Reabsorption rate (%)								
Water	98.41 ±0.33	98.35 ±0.38	98.38 ±0.45	97.94 ±0.56	98.41 ±0.26	97.23** ±0.35	98.29 ±0.41	96.36** ±0.48
Na	97.85 ±0.29	98.10 ±0.37	98.06 ±0.33	97.54 ±0.45	97.96 ±0.46	95.72*** ±0.73	97.77 ±0.28	94.34** ±0.80
K	42.53 ±1.82	44.55 ±2.15	47.97 ±2.40	41.18 ±4.05	44.37 ±3.38	37.11* ±2.85	41.25 ±1.92	31.18*** ±1.80

Values represent means±S.E. of 7 animals. C_{CRE}=creatinine clearance, C_{PAH}=*p*-aminohippuric acid clearance, FF=filtration fraction. *P<0.05, **P<0.01, ***P<0.001, when compared with the before value (paired *t*-test).

Table 2. Effects of benidipine on tubular reabsorptive function in anesthetized SHR

	Vehicle		Benidipine (3 μg/kg, i.v.)	
	before	after	before	after
Urine volume (ml/kg/hr)	5.49±0.23	4.89±0.42	5.13±1.28	8.84±1.81*
Na excretion (μEq/kg/hr)	1216±45	1026±57*	1087±259	1788±390*
K excretion (μEq/kg/hr)	420±25	381±24*	390±58	459±65
C_{CRE} (ml/kg/hr)	245±9	239±10	235±24	243±21
C_{Li} (ml/kg/hr)	142±10	138±11	133±16	172±21*

Values represent means±S.E. of 5 animals. C_{CRE}=creatinine clearance, C_{Li}=lithium clearance. *P<0.05, when compared with the before value (paired *t*-test).

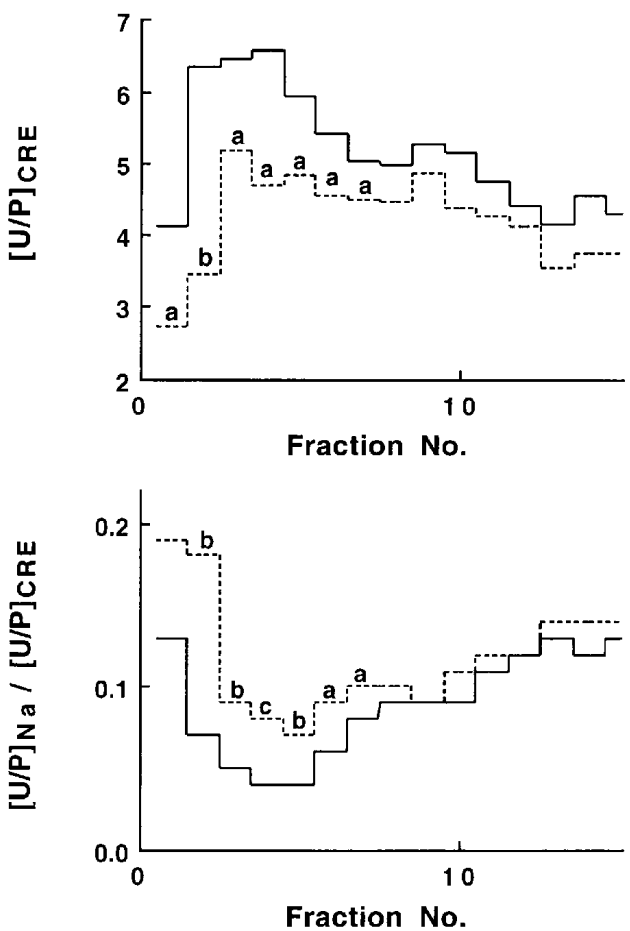

Fig. 1. Effect of benidipine on stop-flow patterns in anesthetized SHR. Solid lines and dotted lines represent stop-flow patterns after the administration of vehicle and benidipine, respectively. Values represent means of 4 animals. $[U/P]_{CRE}$=the ratio of creatinine concentration in urine and plasma; $[U/P]_{Na}/[U/P]_{CRE}$=the ratio of sodium concentration in urine and plasma divided by $[U/P]_{CRE}$. [a]: P<0.05, [b]: P<0.01, [c]: P<0.001, when compared with the vehicle value.

DISCUSSION

In the present study, benidipine significantly increased urine volume and Na excretion with no increase in C_{CRE} in anesthetized SHR (Table 1). These observations indicate that benidipine produces diuresis and natriuresis by inhibition of the reabsorption of water and Na at the tubular site rather than by the increase of GFR. On the other hand, it has been reported that nifedipine (14), felodipine (14), amlodipine (7) and nisoldipine (15) increase GFR in anesthetized SHR. Yokoyama et al. reported that NZ-105, a new calcium antagonist, did not increase GFR at doses that produced diuresis and natriuresis in anesthetized SHR (9). The different effects on GFR among calcium antagonists suggest a difference of vasodilating action in the selectivity for the afferent and the efferent arterioles among each drug. The precise mechanism involved, however, awaits further investigations.

Thomsen (16) has developed the technique of C_{Li} and has validated the concept that under most normal conditions, filtered Li ions at the glomeruli are reabsorbed at the proximal tubule in the same manner as water and Na ions. Consequently, the reabsorption of water and Na at the proximal tubule can be determined, independent from that in the latter nephron segments, by measuring C_{Li}. In the present study, benidipine, at a dose that exhibited diuresis and natriuresis, significantly increased C_{Li} (Table 2), suggesting that benidipine inhibits the reabsorption of water and Na at the proximal tubule. On the other hand, benidipine (3 μg/kg, i.v.) significantly decreased $[U/P]_{CRE}$ and increased $[U/P]_{Na}/[U/P]_{CRE}$ when compared with the vehicle-treated values (Fig. 1). These results indicate that benidipine inhibits the reabsorption of water and Na at the distal nephron. The results from the C_{Li} study and the stop-flow experiment suggest that benidipine produces diuretic and natriuretic effects by inhibiting the reabsorption of water and Na not only at the proximal tubule but also at the distal nephron.

Elevation of intraglomerular pressure precedes and predicts the development of renal disease (17). Intraglomerular hypertension and hyperfiltration have been recognized as important accelerating factors of glomerular injury (18–20). If elevated pressure causes injury, then antihypertensive therapy might lessen the kidney damage by causing systemic and intraglomerular pressure to decline. However, even if systemic blood pressure is decreased by antihypertensive therapy, intraglomerular pressure does not always decrease (21). In fact, hydralazine increases intraglomerular pressure and accelerates glomerulosclerosis in Dahl salt-sensitive rats (22) and SHR (23).

On the other hand, angiotensin converting enzyme inhibitors (ACEI) ameliorate glomerular injury in a variety of

experimental renal diseases, due to a reduction in intraglomerular pressur (24–26). In contrast to ACEI, treatment with calcium antagonists in the renal disease state was originally thought to have adverse effects by preferentially dilating the afferent arteriole and increasing intraglomerular pressure in the reduced number of functioning nephrons (27). In fact, Brunner et al. reported that long-term administration of verapamil worsened glomerular injury in rats with reduced renal mass (28). Wenzel et al. also reported that nitrendipine worsened glomerular injury in rats with renovascular hypertension (29).

Nifedipine (14), felodipine (14), amlodipine (7) and nisoldipine (15) cause dilation more selectively for the glomerular afferent arteriole than the efferent arteriole, as they increase GFR as well as RBF (RPF) in anesthetized SHR. Additionally, Fleming et al. (30), by using video microscopic techniques, found that nitrendipine preferentially dilates the afferent arteriole in the hydronephrotic rat kidney. Thus, it seems that most of the calcium antagonists selectively dilate the afferent arteriole rather than the efferent arteriole.

In the present study, benidipine at 1–10 μg/kg (i.v.) did not increase C_{CRE} (Table 1). On the other hand, benidipine at doses of 3 and 10 μg/kg (i.v.) significantly reduces blood pressure by 10 and 30%, respectively, in anesthetized SHR (Koyanagawa et al., unpublished observation). The reason why benidipine did not increase C_{CRE} may be due to the increase in renal sympathetic nerve activity and the reduction of renal perfusion pressure, resulting from the hypotension induced by benidipine. However, the precise mechanism involved in the inability of benidipine to increase C_{CRE} awaits further investigation. In the present study, benidipine significantly increase C_{PAH} at doses that did not increase GFR, resulting in a significant decrease in FF (Table 1). This observation suggests that benidipine, in contrast to most of the other calcium antagonists, can dilate not only the afferent arteriole but also the efferent arteriole. Therefore, it is expected that benidipine will not produce intraglomerular hypertension and hyperfiltration in patients with renal diseases. In fact, the previous study demonstrated that benidipine inhibits the development of focal segmental glomerular sclerosis in rats induced by puromycin aminonucleoside (31).

In summary, intravenous administration of benidipine produced diuretic and natriuretic effects in anesthetized SHR. The results from the C_{Li} study and the stop-flow experiment demonstrate that benidipine produces diuresis and natriuresis by inhibiting the reabsorption of water and Na at both the proximal tubule and the distal nephron. Benidipine increased C_{PAH} without any change in C_{CRE}, resulting in the decrease in FF. This result suggests that benidipine dilates not only the afferent arteiole but also the efferent arteriole. Thus, benidipine may not accelerate glomerular injury when used to treat patients with renal diseases.

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