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Effect of Felodipine on Renal Hemodynamics and Excretion in the Dog (42086)

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Abstract. The effects of felodipine on renal hemodynamics and excretion were evaluated in the anesthetized dog. Unilateral renal arterial infusion of felodipine produced ipsilateral increases in the absolute and fractional excretion of sodium and water which were greater than those of potassium; these effects occurred in the absence of changes in mean arterial pressure, renal blood flow, or glomerular filtration rate. There were no significant effects on renal hemodynamic or excretory function in the contralateral kidney. The unilateral renal arterial infusion of isotonic saline or vehicle produced no significant effects on renal hemodynamic or excretory function in either ipsilateral or contralateral kidney. Felodipine, a calcium antagonist with vasodilator antihypertensive properties, in doses which do not affect systemic or renal hemodynamics in the dog, increased urinary flow rate and sodium excretion by decreasing renal tubular water and sodium reabsorption. As a vasodilator antihypertensive agent, felodipine possesses potentially advantageous diuretic and natriuretic properties.

Felodipine is an antihypertensive calcium antagonist with vasodilator selectivity. Pharmacologically, it exerts a direct action on phasically active vascular smooth muscle, possibly by interfering with intracellular calcium utilization rather than by inhibition of transmembrane calcium transport (1). At 100-fold higher concentrations than those causing vasodilation in the isolated rat portal vein, a negative inotropic response is obtained in the rat papillary muscle. Expressed in this way the vascular versus cardiac selectivity of felodipine is about six times greater than its structural analog, nifedipine, and about 100 times greater than that of the structurally unrelated calcium antagonist, verapamil (2). In clinical studies, felodipine has a high antihypertensive efficacy (3, 4).

In previous studies in anesthetized normotensive rats and conscious spontaneous hypertensive rats, intravenous administration of hypotensive doses of felodipine increased urinary flow rate and sodium but not potassium excretion; renal micropuncture studies showed inhibition of distal tubular and collecting duct water and sodium but not potassium reabsorption (5, 6). Others have shown that nifedipine increases urinary flow rate, sodium and potassium excretion in dogs (7), and urinary flow rate and sodium but not potassium excretion in humans (8); renal blood flow and glomerular filtration rate were unaffected. Other vasodilator antihypertensive agents, e.g., minoxidil, hydralazine, cause decreases in urinary flow rate and sodium excretion (9, 10).

The current study was undertaken to assess the effects of felodipine on renal hemodynamics and excretion in the dog. To examine the direct renal action of this agent, it was infused into the renal artery of one kidney and bilateral measurements of renal hemodynamics and excretion were made.

Materials and Methods. Male beagle dogs weighing 12–16 kg were anesthetized with sodium pentobarbital 30 mg/kg iv and maintained with sodium pentobarbital 4 mg/kg/hr. Following endotracheal intubation, they were mechanically ventilated with room air to maintain arterial pCO_2 between 35 and 40 mm Hg. Catheters were placed in the jugular veins and a femoral artery for administration of solutions, blood sampling, and arterial pressure measurement. Both kidneys were exposed retroperitoneally by bilateral flank incisions. Electromagnetic flow probes

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were placed on each renal artery and pneumatic occluders were placed distally. Both renal veins and ureters were catheterized and a curved 25-gauge needle connected to a catheter was inserted retrograde into one renal artery for unilateral renal arterial drug infusion. Rectal temperature was kept constant at 37°C with a servo-controlled heating lamp.

At the end of surgery, a priming dose (50 mg/kg) and sustaining infusion (0.75 mg/kg/min) of creatinine were administered with a Ringer-glucose infusion at 2.5 ml/min. At least 60 min were allowed for equilibration and stabilization.

When stable urine flows from both kidneys were obtained, 10-min urine collection periods with midpoint blood sampling were begun. The control phase consisted of three consecutive 10-min urine collection periods. Then, the unilateral renal arterial infusion of 0.9% NaCl (0.5 ml/min infusion rate maintained) was altered as follows: (a) to deliver felodipine (dissolved in 3% polyethylene glycol 400 in 0.9% NaCl) in quantities calculated to achieve a renal vein plasma concentration of 10 nmole/liter based on the prevailing renal plasma flow, $n = 6$; (b) 3% polyethylene glycol 400 in 0.9% NaCl (felodipine vehicle control), $n = 3$; and (c) 0.9% NaCl (isotonic saline control), $n = 2$. The doses of felodipine ranged between 0.50 and 1.50 nmole/min and averaged 1.09 ± 0.13 nmole/min.

Arterial pressure was continuously monitored with an electronic pressure transducer. Heart rate was measured with a tachygraph triggered by the electrocardiogram signal. Mean arterial pressure (MAP), heart rate, and renal blood flow were recorded on a direct-writing polygraph (Beckman RN Dynograph). Occlusive zero flow signals were obtained at the beginning and end of each experiment and periodically during the course of each experiment. The flow probes were calibrated by pumping the dog's own blood at known rates through isolated canine arteries of similar caliber.

Urine and plasma samples were analyzed for creatinine by an automatic analyzer system (COBAS-Bio) employing a colorimetric method (Roche Diagnostic) and for sodium and potassium by flame photometry. Plasma concentration of felodipine was measured by gas chromatography with electron capture (3, 11). Hematocrit was measured with a microcentrifuge. The urinary clearance of creatinine was taken as the glomerular filtration rate (GFR). Renal blood flow (RBF) × (1-Hct) = renal plasma flow (RPF) where Hct = hematocrit. Fractional excretion of substance X (FE_X) = C_X/GFR where C_X is the clearance of $X = U_X V/P_X$ where U_X and P_X are the urine and plasma concentrations of X and V is the urinary flow rate. Filtration fraction (FF) = GFR/RPF.

The data were subjected to analysis of variance with subsequent use of the Bonferroni method for simultaneous multiple comparisons (12). Data in the text, tables, and figures are expressed as means ± SE.

Results. *Felodipine (Fig. 1, Table I).* The renal arterial dose of felodipine, 1.09 ± 0.13 nmole/min, administered on the basis of a precontrol period RPF of 108 ± 13 ml/min, resulted in an actual renal vein plasma felodipine concentration of 13.5 ± 7.0 nmole/

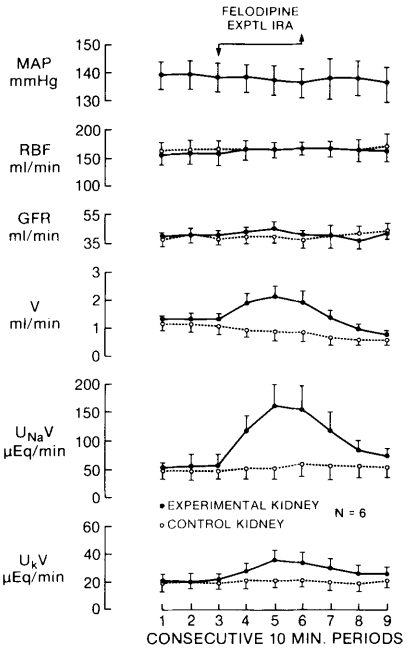

FIG. 1. The effects of unilateral renal arterial administration of felodipine. MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; V, urinary flow rate; $U_{Na}V$, urinary sodium excretion; U_KV, urinary potassium excretion; EXPTL IRA, experimental intrarenal arterial.

TABLE I. SUMMARY OF DATA ON FRACTIONAL EXCRETION OF SODIUM (%)

	Consecutive 10 min periods								
	Control			Experimental[a]			Recovery		
	1	2	3	4	5	6	7	8	9
Felodipine (n = 6)									
Exptl.	0.92 ± 0.26	0.92 ± 0.32	1.02 ± 0.37	1.97 ± 0.61	2.49 ± 0.68*	2.70 ± 0.82*	2.02 ± 0.60	1.63 ± 0.52*	1.26 ± 0.37
Control	0.95 ± 0.35	0.90 ± 0.36	1.01 ± 0.40	1.02 ± 0.42	1.09 ± 0.49	1.26 ± 0.60	1.25 ± 0.64	1.07 ± 0.49	1.01 ± 0.42
Vehicle/saline (n = 5)									
Exptl.	1.64 ± 0.41	1.67 ± 0.42	1.71 ± 0.45	1.73 ± 0.48	1.81 ± 0.45	1.76 ± 0.44	1.68 ± 0.40	1.51 ± 0.28	1.34 ± 0.22
Control	1.83 ± 0.81	1.90 ± 0.78	1.93 ± 0.79	2.01 ± 0.82	2.11 ± 0.70*	1.97 ± 0.70	1.82 ± 0.61	1.74 ± 0.57	1.80 ± 0.61

[a] Drug was infused into renal artery of experimental kidney during periods 4–6.
* $P < 0.05$ versus mean of three control periods.

liter. Felodipine had no major effect on MAP; the small decreases in periods 5 and 6 were significant when compared to the average of control periods 1–3 ($P < 0.05$) but in the vehicle/isotonic saline control experiments (Fig. 2) MAP was likewise significantly decreased in period 5 ($P < 0.05$). There was no effect on RBF or GFR in either kidney. FF ranged between 0.39 ± 0.08 and 0.46 ± 0.06 in the experimental kidney and between 0.38 ± 0.06 and 0.43 ± 0.05 in the control kidney; the changes were not significant. Absolute and fractional water and sodium excretion were significantly increased ($P < 0.05$ for periods 4–7) only in the felodipine infused experimental kidney; they were unchanged in the contralateral control kidney. Absolute potassium excretion was significantly increased ($P < 0.05$ for periods 4–6) only in the felodipine infused experimental kidney. The increase in potassium excretion was less than that in sodium excretion and was similar to that seen in periods 5 and 6 in the control kidney of the vehicle control experiments (Fig. 2).

Vehicle/isotonic saline (Fig. 2, Table I). The results from the 3% polyethylene glycol 400 in 0.9% NaCl (felodipine vehicle control) and the 0.9% NaCl (isotonic saline control) studies were similar and the results have been pooled. There were no significant effects on RBF, GFR, FF, absolute and fractional sodium excretion in either kidney. MAP was significantly decreased in period 5 only ($P < 0.05$). Absolute water excretion was significantly decreased from both kidneys in period 7–9 ($P < 0.05$) and absolute potassium excretion was increased in the control kidney in periods 5, 6, and 8 ($P < 0.05$).

Discussion. These studies demonstrate that unilateral renal arterial infusion of felodipine produces an ipsilateral diuresis and natriuresis that is unaccompanied by changes in MAP, RBF, or GFR; urinary potassium excretion is little affected. The increases in urinary flow rate and sodium excretion occurred in the face of an unchanged filtered water and sodium load indicating that felodipine decreased net renal tubular water and sodium reabsorption. With unchanged systemic and renal hemodynamics, it is unlikely that changes in intrarenal physical forces occurred suggesting that the diuretic and natriuretic

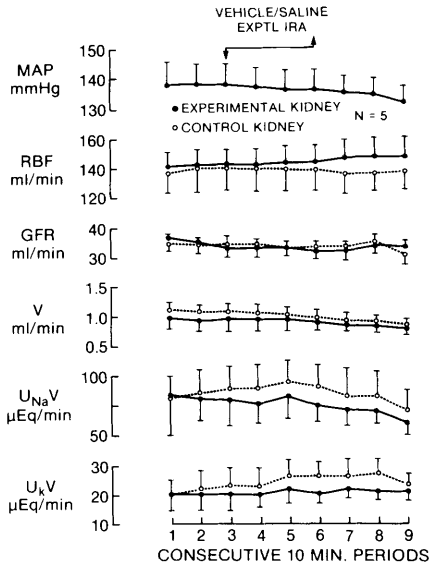

FIG. 2. The effects of unilateral renal arterial administration of vehicle/isotonic saline. Abbreviations as in legend for Fig. 1.

effect of felodipine is due to a direct effect on renal tubular epithelial cell sodium and water transport. In contrast, the vasodilator antihypertensive agents, hydralazine [(9, 10) personal observations] and minoxidil (9), produce decreases in absolute and fractional water, sodium, and potassium excretion with little change in systemic or renal hemodynamics indicating an increase in net renal tubular water, sodium, and potassium reabsorption.

These results with felodipine in the dog are similar to those observed in the anesthetized normotensive rat wherein low dose intravenous felodipine administration produced a diuresis and natriuresis without changes in MAP, RBF, or GFR; renal micropuncture studies showed an inhibition of distal tubular and collecting duct water and sodium reabsorption without any change in single nephron GFR or potassium excretion or reabsorption (5). In conscious spontaneous hypertensive rats (SHR), bolus intravenous injections of felodipine produced dose-related decreases in MAP and renal vascular resistance which were associated with increases in RBF, GFR, urinary flow rate, and sodium excretion; urinary potassium excretion was not affected (6). The increases in urinary flow rate and sodium excretion were in excess of what could be accounted for by the increases in filtered water and sodium load (i.e., fractional water and sodium excretion increased) indicating that felodipine decreased net renal tubular water and sodium reabsorption. In view of the well-known effects of renal perfusion pressure on urinary flow rate and sodium excretion (13), it was observed that nearly maximum increases in urinary flow rate and sodium excretion were observed at the felodipine dose which produced a nonsignificant lowering (−3%) of MAP and that the diuretic and natriuretic responses were attenuated at the higher felodipine doses which produced substantial lowering of MAP (−37%). Thus, the renal effects of felodipine in the dog are similar to those in the rat: (a) a significant diuresis and natriuresis due to a decreased water and sodium reabsorption in distal tubule and collecting duct, (b) occurring independently of changes in systemic or renal hemodynamics, (c) little effect on potassium excretion and reabsorption.

Nifedipine, a structural analog of felodipine, has been examined in the dog and rat. Unilateral renal arterial infusion of nifedipine in the anesthetized dog (7) produced a dose-related increase in urinary flow rate, sodium, potassium, chloride, calcium, and magnesium excretion without changes in RBF or GFR; MAP was unaffected at the lowest nifedipine dose (1 μg/min) but was significantly decreased at the two higher nifedipine doses (5 and 20 μg/min).

In conscious SHR (6), bolus intravenous injections of nifedipine produced dose-related decreases in MAP and renal vascular resistance which were associated with increases in RBF, GFR, urinary flow rate, and sodium excretion. The duration of the diuresis and natriuresis appeared shorter with nifedipine than with felodipine. Fractional water and sodium excretion were increased, indicating a decrease in net renal tubular water and sodium reabsorption; urinary potassium excretion was not affected. In contrast, vasodilator antihypertensive, minoxidil, produced decreases in MAP, RBF, GFR, absolute and fractional excretion of water, sodium, and potassium indicating an increase in net renal

tubular water, sodium, and potassium reabsorption. Similar results with minoxidil have been reported by others (9).

Thus, felodipine produces a diuresis and natriuresis at doses which do not affect MAP, RBF, or GFR. This is in contrast to other vasodilator antihypertensive agents, hydralazine and minoxidil, which produce antidiuresis and antinatriuresis resulting in sodium and water retention which can limit their effectiveness in the treatment of hypertension. As a vasodilator antihypertensive agent, felodipine possesses potentially advantageous diuretic and natriuretic properties (14).

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