Natriuretic Action of Manidipine Hydrochloride, a New Calcium Channel Blocker, in Spontaneously Hypertensive Rats

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Abstract—Effects of manidipine, a new dihydropyridine derivative, on sodium and water excretion were examined in conscious spontaneously hypertensive rats. Manidipine (3 mg/kg) significantly increased the sodium and water excretion in the urine collected for 3 hr after the calcium antagonist was orally administered, and its natriuretic action was more prominent than those of nifedipine and nicardipine (3 mg/kg). These results suggest that manidipine may be useful for treating hypertension.

Manidipine (CV-4093·2HCl) shows potent and long-lasting antihypertensive action, dilates renal vasculature, and increases renal blood flow in spontaneously hypertensive rats (1, 2). The calcium antagonist also causes highly selective long-lasting inhibition of the calcium currents in the smooth muscle cells of the rabbit pulmonary artery but has little cardiodepressant action (3, 4). In the present experiments, the effect of manidipine on urinary excretion of electrolytes and water was examined in spontaneously hypertensive rats.

Male spontaneously hypertensive rats (SHR) of a stroke-prone strain were used at 10–11 weeks of age (systolic blood pressure: 205±2 (S.E.) mmHg; body wt.: 236±2 g). The rats were housed in groups of 5 to 7 animals in wire-mesh cages in a temperature-and light-controlled room and were allowed free access to food and tap water. On the day of the experiment, the rats were fasted for 2 hr prior to saline loading. Calcium antagonists (manidipine hydrochloride, nifedipine, nicardipine hydrochloride), synthesized in our Chemistry Research Laboratories, were suspended in 5% arabic gum and orally administered at the volume of 0.2 ml/100 g body wt.; and immediately after the drug administration, a volume of 0.9% saline equivalent to 2.5% of the body wt. was orally administered to the animals (n=5–7 in each group). After the saline loading, 3-hr urine samples were collected using metabolism cages. Sodium and potassium concentrations in urine were analyzed using flame photometry (Corning 455), and creatinine concentration in the urine was measured using an assay kit (Wako). The experiment was done twice, once with manidipine and nifedipine and once with nicardipine. A control was used in each experiment.

As shown in Fig. 1, manidipine (3 mg/kg, p.o.) and nifedipine (3 mg/kg, p.o.) increased urinary volume to 270% and 217% of the value in the control group (0.90±0.20 ml/100 g body wt.), respectively, and also increased sodium excretion to 217% and 165% of the control value (150±4 uEq/100 g body wt.), respectively. The sodium excretion in the rats treated with manidipine was significantly higher than that in rats treated with nifedipine. Nicardipine (3 mg/kg, p.o.) did not increase urinary volume (0.97±0.08 ml/100 g in the control and 0.98±0.12 ml/100 g in the treated group) or sodium excretion (161±27 μEq/100 g in the control and 160±28 μEq/100 g in the treated group).

Potassium excretion was not changed by treatment with any of the calcium antagonists (values in controls: 75±5 and 84±8 μEq/100 g). Urinary excretion of creatinine was slightly, but significantly, increased by the administration of manidipine and nifedipine: the values were 0.41±0.02 (n=5), 0.48±0.01
Fig. 1. Effects of manidipine, nicardipine and nifedipine on urinary excretion of sodium, potassium and water in spontaneously hypertensive rats. UV: urine volume, UNaV: sodium excretion, UKV: potassium excretion. Dose: 3 mg/kg (p.o.). Mean±S.E. n=5-7. ** and *** P<0.01 and 0.001 (vs. control). Statistical differences were evaluated using Student’s t-test and Dunnett’s t-test. The experiment was done twice, and a control was used in each experiment. The control values were 0.90±0.20 and 0.97±0.08 ml/100 g body wt. for urinary volume, 150±4 and 161±27 μEq/100 g for sodium excretion, and 75±5 and 84±8 μEq/100 g for potassium excretion.

(n=5, P<0.05 vs. control using Dunnett’s t-test), and 0.46±0.01 (n=5, P<0.05 vs. control) mg/100 g in the control, manidipine, and nifedipine treated groups, respectively. This suggests that both calcium antagonists may slightly increase the glomerular filtration rate in the kidneys of SHR. Nicardipine had no effect on the excretion of creatinine (0.45±0.02 and 0.42±0.04 mg/100 g in the control and treated groups, respectively).

The alteration of renal hemodynamics and function is one of the most important factors involved in the mechanism for developing and maintaining high blood pressure. A lowered ability to excrete sodium and water results in an increase in circulatory fluid volume and enhancement of vascular reactivity to vasoactive substances (5–7). The reduction in blood pressure induced by antihypertensive treatment has a negative effect on the sodium and water excretion due to the decrease in renal perfusion pressure. Therefore, natriuretic action observed in the present experiments suggests the usefulness of the calcium antagonists in the treatment of hypertension.

Manidipine dilates renal resistance vessels, inhibits renal vascular contractions induced by vasoactive substances, and effectively increases renal blood flow in the rats with spontaneous hypertension (2). Manidipine showed more marked diuretic action, compared with nifedipine and nicardipine in SHR, at least at the dose used in this experiment. It has been reported that nicardipine exerts diuretic action in dogs (8). In the present experiment, we used one dose of nicardipine, 3 mg/kg (p.o.). Hypotensive action at this dose of nicardipine was weaker than those of the other calcium antagonists (1). Therefore, the effect of higher doses of nicardipine on water and electrolyte excretion should be examined in SHR in future experiments. In the present study, urine samples were collected for only the first 3 hr after the administration of calcium antagonists. Since manidipine shows a much longer duration of hypotensive action than the other calcium antagonists in SHR (1), its natriuretic action is expected to last longer than those of the other calcium antagonists. Although the
detailed mechanism remains unknown, the natriuretic action of manidipine seems to be due partly to the increase in renal blood flow induced by the calcium antagonist, and it seems that it would be beneficial in treating hypertensive patients.

References