Renal Effects of Prostaglandin E1 in Hypertensive Patients

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ABE, K., OTSUKA, Y., SAITO, T., MIYAZAKI, S., YASUJIMA, M., IROKAWA, N., SEINO, M., CIBA, S. and YOSHINAGA, K. Renal Effects of Prostaglandin E1 in Hypertensive Patients. Tohoku J. exp. Med., 1975, 116 (4), 351–358 — The effects of prostaglandin E1 on fluid and sodium excretion, creatinine clearance and renin release were examined in 26 hypertensive patients including 9 cases of essential hypertension, 10 of renovascular hypertension and 7 of primary aldosteronism. When prostaglandin was infused intravenously in a total dose of 120 µg in 60 min, urine volume was increased in 70% of cases, and sodium excretion in 61%, but little changes were observed in creatinine clearance. The most prominent diuresis and natriuresis were obtained in primary aldosteronism (mean increase was 319% in urinary volume, and 222% in sodium output). The average increase in urinary volume were 61% in patients with essential hypertension and 97% in renovascular hypertension. And urinary output of sodium was increased by 63% in the former and 56% in the latter. The remarkable renal effects of prostaglandin E1 in primary aldosteronism were completely abolished after the administration of spironolactone. Significant elevation of plasma renin activity resulted from prostaglandin E1 infusion in essential hypertension, while no constant effect was obtained in renovascular hypertension and primary aldosteronism. The present experiments indicate that prostaglandin E1 has different effects on the kidney according to the types of hypertension and the effects correlate closely with patient’s status of extracellular fluid volume or sodium balance.

It has been well known that vaso-dilator lipid, prostaglandin (PG), produces an increase of renal blood flow, urinary output and urinary excretion of sodium in animal and man (Johnston et al. 1967; Vander 1968; Lee et al. 1971). Recently, Lee (1971, 1972) proposed a hypothesis that PGA may be a circulatory natriuretic antihypertensive hormone of renal origin. On the other hand, it has also been suggested that PGE2 may be a modulator of the excretory function of the kidney (Fulgraff et al. 1974). In the present study, the effects of prostaglandin on the renal handling of water and electrolytes, and on the secretion of renin have been investigated in various types of hypertension.

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MATERIALS AND METHODS

Twenty-six patients with various types of hypertension were included in this study. They consisted of 9 cases of essential hypertension, 10 of renovascular hypertension (6 cases of them underwent surgical operation with excellent results), and 7 of primary aldosteronism which were cured by removal of adrenocortical adenoma. All patients were studied in Tohoku University Hospital. The diagnosis had been confirmed with physical and laboratory examinations, intravenous pyelography, radioisotope renography, and determination of plasma 11-OHCS, plasma renin activity, plasma aldosterone level, urinary catecholamine and vanillylmandelic acid. They were 13 men and 13 women ranging in age from 12 to 58 years with an average of 33.6. They had blood pressure of 150 mmHg in systolic and 90 mmHg in diastolic or higher on repeated observations. There was no evidence of severe hypertensive complications in cardiovascular renal organs. All patients were allowed to take ordinary diet containing approximately 250 mEq of sodium per day, and every antihypertensive drug had been discontinued at least 2 weeks prior to study.

After an over-night fast, PGE₁, diluted in 5% glucose to a concentration of 1 μg/ml, was infused intravenously at three rates of 1, 2, and 3 μg/min by means of a constant perfusion pump in a total dose of 120 μg for 60 min. In control study, the vehicle (5% glucose solution) was infused for the same length of time. The blood pressure was determined every 3 min using the sphygmomanometer. One hour urines before and during prostaglandin E₁ infusion were collected, and the concentrations of sodium and potassium were determined. Glomerular filtration rate was measured as creatinine clearance. Sampling of blood for measurement of renin activity was done from antecubital vein before and during the infusion. Plasma renin activity was measured by radioimmunoassay of angiotensin I (Abe et al. 1971).

RESULTS

Depressor effect of PGE₁

Systemic blood pressure was lowered by the intravenous infusion of PGE₁ in all patients except one with renovascular hypertension in whom blood pressure was not changed. Fig. 1 demonstrates the changes of mean blood pressure when PGE₁ was infused at a rate of 0.05 μg/kg/min. The per cent decreases of mean blood pressure in each type of hypertension were as follows; 19.3±4.5% in 7 cases of essential hypertension, 19.6±6.6% in 7 renovascular hypertension, and 26.4±3.9% in 6 primary aldosteronism. There was no significant difference between the decrease of blood pressure in essential hypertension and renovascular hypertension. In primary aldosteronism, however, greater reduction of blood pressure than those in the former two types of hypertension was observed.

Renal effects of PGE₁

Fig. 2 demonstrates the per cent increase or decrease of urine volume, urinary sodium and potassium excretion, and creatinine clearance following PGE₁ infusion. In the control study (infusion of 5% glucose for 60 min), small changes of less than 20% were observed in these parameters. Therefore, the changes more than 20% were defined as positive effects of PGE₁.

Urine volume was increased in 16 cases (70%) out of 23. A remarkable increment was found in primary aldosteronism in which 4 out of 7 had an
Fig. 1. Effect of prostaglandin E₁ (PGE₁) on mean blood pressure in hypertensive patients. Changes of mean blood pressure in 21 patients with various types of hypertension (left), and the reduction rates of average mean blood pressure in essential hypertension (EH), renovascular hypertension (RVH) and primary aldosteronism (PA) (right) following PGE₁ infusion are illustrated. Numbers in the parentheses indicate the numbers of the patients studied.

Fig. 2. Effect of PGE₁ on renal function in hypertensive patients. Changes of urinary volume (ΔUV), urinary excretion of sodium (ΔUNaV) and potassium (ΔUKV) and creatinine clearance (ΔGFR) following PGE₁ infusion are shown. Open circles indicate primary aldosteronism.
augmentation beyond 100%. On the other hand, urinary output was decreased in 3 cases (13%) and not changed in the remaining 4 (17%). Increased sodium excretion was found in 14 cases (61%). A prominent increase was also found in primary aldosteronism. Sodium output was doubled or higher in 5 cases (71%). Urinary excretion of sodium was decreased in only 2 (9%), and no significant change was found in the remaining 7 (30%). Marked increase of potassium excretion was observed in only 4 cases in which 2 belonged to primary aldosteronism. No significant alteration of creatinine clearance was obtained in 13 cases (57%), while the remaining 10 had a slight increment or decrement.

In essential hypertension, the increase of urine volume was found in 6 out of 7 cases and sodium excretion in 4 cases. Similar changes were observed in renovascular hypertension. In primary aldosteronism, augmentation of both fluid volume and urinary sodium was obtained in almost all patients. Fig. 3 demonstrates the average increase ratio of urine volume and sodium excretion in them. The greatest increment among 3 types of hypertension was found in primary aldosteronism (319% in urine volume and 222% in sodium output). On the other hand, essential hypertension had the average increment of 61% in volume and 63% in sodium, and renovascular hypertension, 97% and 56% respectively.

To investigate the mechanism by which the prominent effect of PGE₁ was induced in primary aldosteronism, the same doses of PGE₁ were infused intravenously in a case of this disease after the administration of spironolactone 150 mg daily for 14 days. Fig. 4 demonstrates the comparison of the changes of urine volume, urinary sodium excretion and creatinine clearance during PGE₁ infusion before and after the administration of spironolactone. Remarkable diuretic and natriuretic effects of PGE₁ were abolished after the medication.

Fig. 3. Average increases of urinary volume (ΔUV) and urinary sodium output (ΔUNaV) in essential hypertension, renovascular hypertension and primary aldosteronism. Numbers in the parentheses indicate the numbers of the patients studied.
Fig. 4. Comparison of the changes of urine volume, urinary sodium excretion and creatinine clearance during prostaglandin E₁ infusion before and after the administration of spironolactone in a case of primary aldosteronism. □, aldactone A(-); □□, aldactone A (100 mg/day).

Effect on renin release

Plasma renin activity was measured in 23 cases of various types of hypertension. Fig. 5 shows the changes of peripheral vein blood renin activity following infusion. In 8 cases of essential hypertension, marked increase of the activity...
Fig. 6. Average plasma renin activity before and during prostaglandin E₁ infusion in 8 cases of essential hypertension (EH), 8 of renovascular hypertension (RVH) and 7 of primary aldosteronism (PA). Open columns represent the plasma renin levels before prostaglandin E₁ infusion and mist columns those after infusion.

was found in 3 cases and moderate in 4, while the remaining one showed unaltered plasma renin activity. The augmentation of renin secretion was obtained in 4 out of 8 cases of renovascular hypertension, while in the remaining 4 renin activity was decreased. In primary aldosteronism, no alteration in renin secretion was found in all cases.

Fig. 6 demonstrates the average plasma renin activity before and during PGE₁ infusion in each type of hypertension. In essential hypertension, the

Fig. 7. Relationship between the changes in plasma renin activity and the alterations in urine volume ($\Delta V$), urinary sodium output ($\Delta U_{NaV}$) and creatinine clearance ($\Delta GFR$).
average values increased from 10.3±2.9 (s.e.) to 21.3±6.5 ng/ml, while PGE₁ induced no significant increment of renin secretion in the remaining 2 types. The average values in renovascular hypertension were 15.3±4.6 in control period and 15.9±5.7 after PGE₁ infusion, and in primary aldosteronism, 2.4±0.6 in control and 2.7±0.2 ng/ml after.

Fig. 7 demonstrates the relationship between the changes of plasma renin levels and the alteration in urine volume, urinary sodium, creatinine clearance during PGE₁ infusion. No correlation was found among them.

**DISCUSSION**

The present experiments demonstrate that PGE₁ exerted the prominent effects on the renal functions in hypertensive patients as previously reported in experimental animals. In many patients, the natriuresis mediated by PGE₁ was associated with a parallel increase in water excretion, but these increments were not accompanied by any significant changes in creatinine clearance. These data indicate that the effects of PGE₁ on urinary fluid and sodium output are not caused by the increase in glomerular filtration, but rather by a direct or indirect action on renal tubular reabsorption. There are many factors except glomerular filtration rate which are involved in renal handling of sodium and water; electrolytes balance, extracellular fluid volume, intrarenal distribution of blood flow, aldosterone, and physical factors. Prostaglandin E₁ has been well known to produce an increase of renal blood flow (Johnston et al. 1967). Furthermore, it has also been revealed by us that PGE₁ inhibits the reabsorption of fluid in human proximal tubules (Abe et al. 1974). Therefore, it is likely that inhibitions of water and sodium reabsorption by PGE₁ are attributable almost entirely to the physical factors such as peritubular hydrostatic pressure.

In the present study, obvious difference in the degree of renal effects of PGE₁ among 3 types of hypertension was found. The greatest increase in water or sodium excretion was obtained in primary aldosteronism. However, those increments were abolished after administration of spironolactone. This result indicates that the diuretic or natriuretic effects of PGE₁ are dependent on the extracellular fluid volume or sodium balance in the body.

Concerning the effects of PG on renin release, opinions of investigators have been controversial. Vander (1968) and Carlson et al. (1969) described that no constant or significant changes of plasma renin activity were obtained when PGE₁ was infused in dogs or men, while Werning et al. (1971) found that following the infusion of PGE₁ in dogs there was a significant increase in plasma renin activity accompanied by a marked increase in diuresis and natriuresis. This discrepancy seems to come from the differences of PG, and duration of PG infusion or the amount of PG given. The present experiment indicates that PGE₁ exerts different influences on renin release according to the types of hypertension. Although the excretion rates of sodium and water during PGE₁ infusion in essential hypertension were similar to those in renovascular hypertension, significant difference in renin
secretion was observed between the two groups. What is the cause of this difference? This question seems to be very important, but it remained unanswered in the present study, because we found no correlation between the changes in renin, water and sodium excretion, and glomerular filtration following the infusion of PGE$_1$.

References


