ROLE OF PROSTAGLANDINS IN CAPTOPRIL-INDUCED NATRIUREESIS

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Summary

To determine whether prostaglandins (PG) contribute to captopril-induced natriuresis, 20 hypertensive subjects were assigned to one of the following three groups: group a, captopril (C) administration; group b, C + indomethacin (I); group c, I alone. Captopril was given in a dose of 100, 200, 400mg/day and indomethacin in a dose of 100mg/day for one week. In group a (n=10), natriuresis was clearly increased in the seven day periods with captopril in a dose of 200 and 400mg/day but not at 100mg/day. After captopril 200 or 400mg/day, but not 100mg/day, urinary PGE_2 and PGI_2 excretion significantly increased while filtration fraction fell due to a rise in renal plasma flow. Plasma aldosterone (PA) significantly decreased after C(p<0.05). In group b (n = 7), natriuresis disappeared during captopril 200 or 400mg/day and indomethacin administration even when PA decreased as in group a. In group c (n = 3), natriuresis was unchanged. In conclusion, natriuresis by C is critically dependent upon increased secretion of PG.

Introduction

Captopril (C), unlike the other non-diuretic antihypertensive drugs generally produces mild to moderate natriuresis in spite of its potent hypotensive effect [1,2]. Several authors [3,4] have demonstrated that C increases plasma immunoreactive prostaglandin (PG) secretion in healthy and hypertensive subjects. It is known that PG may function as natriuretic factors under physiological and pharmacological conditions [5].

Our purpose was to determine the role of PG in mediating the captopril-induced natriuresis in hypertensive patients both by measuring the changes in urinary PG excretion after C and by assessing the effect of PG synthetase inhibition on the natriuretic response to captopril.
Patients and methods

Twenty patients with essential hypertension were hospitalised during the study. In all subjects a moderate to mild hypertension (diastolic blood pressure 95—110 mg/Hg) had been documented for at least six months in an outpatient setting. Antihypertensive drugs were discontinued at least 10 days before hospitalisation. The diagnosis of essential hypertension was based upon the absence of known aetiologies as assessed by urinary catecholamines, plasma aldosterone and renin activity, intravenous pyelogram and, whenever indicated, renal arteriogram and renal vein renin activity.

All subjects were men. Their mean age (±SE) was 41.4 ± 3.1 years. In all subjects creatinine clearance was greater than 80ml/min. Before C administration, all subjects ingested constant isocaloric diets containing 100mEq of sodium and 1,200mg of phosphorous daily until metabolic balance was achieved (usually by the fifth hospital day). Blood pressure was recorded twice a day at 8 am and 4 pm and the mean of these two values was taken as representative of that day. Average blood pressure (BP) on admission was 158/104 (±8/4SE).

The subjects were assigned to one of three groups after a three day baseline period. Group a: 10 subjects received C for seven days. Group b: subjects were given indomethacin (I) plus C for seven days. Group c: three subjects received only I. Captopril was given in a dose of 100, 200 or 400mg/day and indomethacin in a dose of 100mg/day given in four divided daily doses (at 8 am, at 2 pm, at 8 pm and 2 am).

Blood was taken at 8 am every day in both the baseline and the experimental period, after overnight recumbency and fasting, for creatinine and electrolyte (sodium, potassium, phosphorous) determination. Blood samples for plasma aldosterone were drawn after two hours of upright position in the last day of baseline and experimental periods and were collected on ice, centrifuged and separated immediately. Twenty-four-hour urinary excretion of electrolytes and creatinine was determined daily. Twenty-four hour urinary excretion of PGE$_2$ and 6-keto-prostaglandin F$_1\alpha$ as well as PAH clearance were determined only in the last day of baseline and experimental period. For PG measurement, urine was refrigerated immediately after collection and stored at —20°C until assayed.

Plasma aldosterone was measured by specific radioimmunoassay (Sorin Biomedica, Saluggia). Sodium and potassium were measured by flame photometry, creatinine by a Beckman autoanalyser and phosphorous by Subarrow’s method. Measurement of PGE$_2$ and 6-keto-PGF$_1\alpha$ (the stable hydrolysis product of prostacyclin) in urine was carried out according to Ciabattoni et al [6] with minor variations.

Results were expressed as mean ± SEM. Two tailed Student’s ‘t’ test was used for statistical comparisons of the means.

Results

Group a. Captopril at 200 and 400mg/day caused a significant rise in urinary Na$^+$ excretion, but not at 100mg/day (Figure 1). The difference from the mean

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baseline excretion averaged 26.9 ± 4.7 and 25.7 ± 0.9 mEq/day in the seven day periods at the dosage of 200 and 400 mg/day, respectively. In the seven patients with captopril-induced natriuresis, ΔU Na+ V significantly correlated with ΔU HPO4 V (p<0.01). After captopril 200 or 400 mg/day, but not 100 mg/day, the urinary excretion of PGE2 and 6-keto-PGF1α significantly increased (6.2 ± 2.1 ng/hr pre-C, 15.1 ± 3.3 ng/hr after, p<0.05; 11.8 ± 3.2 ng/hr pre-C, 25.0 ± 8.1 ng/hr after, p<0.05, respectively) in conjunction with the increase in renal plasma flow (530 ± 7 ml/min pre-C, 670 ± 10 ml/min after, p<0.001). The glomerular filtration rate, calculated as creatinine clearance, showed no change. PA significantly decreased after C (257.7 ± 69.9 pre-C, 166.6 ± 38.4 pg/ml after, p<0.05). Mean systolic and diastolic BP decreased from 159 ± 10 up to 132 ± 8 and from 116 ± 6 to 91 ± 5 mmHg (p<0.01).

Group b. The administration of captopril (200 and 400 mg/day) plus indomethacin (100 mg/day) induced minimal changes in sodium excretion (p>0.05) (Figure 2) even if PA significantly decreased (270.7 ± 62.1 pre, 193.6 ± 51.8 pg/ml
after; \( p < 0.05 \). Urinary excretion of \( \text{PGE}_2 \) and 6-keto-PGF\(_{1\alpha}\) significantly decreased (7.1 ± 1.8ng/hr pre, 3.5 ± 0.6ng/hr after, \( p < 0.05 \); 11.1 ± 1.9ng/hr pre, 4.7 ± 1.5ng/hr post, \( p < 0.05 \) respectively). In this group administration of captopril plus indomethacin did not modify creatinine and PAH clearance. Mean systolic and diastolic BP significantly decreased from 154 ± 8 to 140 ± 5 and from 113 ± 4 to 101 ± 3mmHg respectively (\( p < 0.05 \)).

**Group c.** Administration of indomethacin (100mg) did not modify sodium excretion (Figure 2), creatinine and PAH clearance, and mean BP while significantly decreasing urinary excretion of \( \text{PGE}_2 \), 6-keto-PGF\(_{1\alpha}\) and PA.

![Graph showing changes in sodium excretion with captopril and indomethacin](image)

Figure 2. Deviations in \( U_{\text{Na}}V \) from average baseline value caused by administration of captopril plus indomethacin and indomethacin alone

**Discussion**

This study confirms that captopril increases urinary sodium excretion in hypertensive patients even while reducing blood pressure [1,2]. *Group a* studies
indicate that this natriuresis, due to decreased tubular reabsorption, occurs in patients treated with high doses of captopril (200–400 mg/day), but not with low doses (100 mg/day) and is associated with increased urinary PGE₂ and PGI₂ excretion and PAH clearance. As expected [1], plasma aldosterone significantly decreased after captopril. Group b studies were undertaken to verify the effect of PG inhibition on captopril-induced natriuresis. The results show that indomethacin fully antagonises this natriuresis even if the fall in plasma aldosterone is maintained as in group a. Finally, group c studies exclude that changes in tubular handling of sodium are the consequence of a direct, pharmacological action of indomethacin on the tubule.

Therefore, from our findings we can conclude that the C-dependent natriuresis is secondary to increased secretion of PGE₂ and PGI₂ and is independent of the simultaneous reduction in plasma aldosterone. The close correlation between natriuresis and phosphaturia suggests that the proximal tubule is the main site of decreased sodium reabsorption. The reduced filtration fraction may account for sodium rejection at this tubule site. In agreement with our findings, animal studies have shown that the natriuresis induced by administration of arachidonic acid and vasodilatory PG is secondary to changes in renal haemodynamics causing alterations in peritubular hydrostatic and oncotic pressure and thereby affecting proximal tubular reabsorption [5].

References