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THE EFFECT OF FELODIPINE A NEW CALCIUM ANTAGONIST ON RENAL FUNCTION

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Summary

Felodipine, a structural analogue of Nifedipine is a potent peripheral arteriolar vasodilator. In a double-blind placebo controlled study we have investigated the effect of this drug on renal haemodynamics, sodium excretion and renal prostaglandin synthesis. Nine normal male volunteers were studied in the presence and absence of Indomethacin. No significant change in renal plasma flow or glomerular filtration rate was found. A significant diuresis and natriuresis followed Felodipine administration which was not abolished by prior treatment with Indomethacin. No significant change in urinary 6-keto-$PGF_{1\alpha}$ excretion was found. It seems most likely that the diuretic effects of the drug are mediated by a direct effect on tubular sodium transport.

Introduction

Calcium antagonists are widely prescribed in the therapy of hypertension on the basis of their vasodilating properties. Unlike most vasodilators there is evidence that Verapamil and Nifedipine, two structurally dissimilar calcium antagonists, promote renal excretion of sodium and water [1,2]. Felodipine is a structural analogue of Nifedipine but differs in two respects. It has less negative inotropic effect on cardiac muscle and is therefore a more selective peripheral arteriolar vasodilator [3], secondly, it is not thought to inhibit transmembrane calcium flux but acts at an intracellular site, possibly competing with calcium for binding sites on Calmodulin [4]. Natriuresis is an unusual property for a vasodilator and one which is potentially useful in a drug whose antihypertensive potency compared favourably with Minoxidil in a recent crossover trial [5]. We were therefore interested to investigate whether Felodipine, like Nifedipine, increased sodium excretion, and whether, in the event that it did so, this was associated with a change in renal blood flow or urinary prostaglandin excretion, these being two potential mechanisms of mediating a natriuretic response.

Methods

Nine normal male volunteers were studied after giving informed consent; the study was double-blind and placebo-controlled. Felodipine was administered in the presence and absence of Indomethacin, the third part being a double-placebo control. At least one week elapsed between the three parts of the study in each volunteer. Subjects were requested to abstain from alcohol, caffeine-containing drinks, analgesics and sexual activity for 24 hours prior to each study. Twelve hours before attendance Indomethacin (50mg) or placebo was taken. At 0900 hours on the day of the study intravenous cannulas were placed in both arms and bolus injections of PAH (0.4gm) and Inulin (2.3gm) were given. Thereafter a continuous infusion of PAH (20mg/min) and Inulin (18mg/min) in a volume of 1ml/min was maintained throughout the study. Subjects maintained an oral water intake of 200ml/hour, and remained supine, standing only to void urine. After one hours equilibration a further dose of Indomethacin (50mg/placebo) was administered and a one hour control period ensued; following the control period Felodipine (0.075mg/kg) was taken by mouth and sampling of blood and voided urine continued at 30 minute intervals for two-and-a-half hours.

Arterial blood pressure and pulse rate were monitored at 15 minute intervals using an automatic blood pressure recorder. Glomerular filtration rate and renal plasma flow were estimated by clearance of Inulin and PAH, these being measured by standard colorimetric assay. Sodium and potassium were measured by flame photometry. 6-keto-$PGF_{1\alpha}$ was measured in urine by a radio-immunoassay.

Results

Heart rate increased from 60bpm to 74bpm ($p<0.001$) 30 minutes after Felodipine. There was no change in systolic blood pressure; diastolic blood pressure fell one hour after Felodipine from 74mmHg to 68mmHg ($p<0.02$).

No significant change in PAH or Inulin clearance occurred in any of the three groups nor was there a trend in any group that did not reach statistical significance. Filtration fraction similarly showed no significant change.

The changes in urine volume and urine sodium excretion are illustrated in Table I. Felodipine caused a significant increase in urine flow that was maximal at 60 minutes; pre-treatment with Indomethacin caused a significant delay in this diuresis. Free-water clearance followed an identical pattern to urine volume. Urine sodium excretion increased twofold, the response being maximal at 90 minutes; Indomethacin had no significant effect on natriuresis.

Urine potassium excretion remained constant and calcium excretion followed a similar pattern to sodium. There was no change in plasma renin activity.

Table II illustrates the excretion of urinary 6-keto-$PGF_{1\alpha}$ assayed at control, at 90 minutes, (the time of peak sodium excretion) and at 150 minutes. 6-keto-$PGF_{1\alpha}$ is suppressed by Indomethacin; there is no change in excretion following Felodipine.

TABLE I. Urine volume and urine sodium excretion. Values expressed as Mean ± SEM

		Control	30 min	60 min	90 min	120 min	150 min
Urine Volume ml/min	Felodipine + Placebo	6.0 ±0.2	9.5† ±0.5	10.1*** ±0.7	8.7*** ±0.5	6.4 ±0.8	5.2 ±0.3
	Felodipine +Indomethacin	6.1 ±0.9	6.5 ±0.9	9.4 ±0.9	9.3*** ±1.2	7.5 ±1.3	7.2 ±0.6
	Placebo + Placebo	6.2 ±1.1	7.2 ±1.1	6.3 ±0.9	5.2 ±0.7	5.9 ±0.5	7.3 ±0.7
Urine Sodium μmol/min	Felodipine + Placebo	323 ±26	426 ±53	554* ±67	679** ±115	467* ±45	445 ±35
	Felodipine +Indomethacin	321 ±37	352 ±60	493 ±87	575* ±97	492 ±107	466 ±73
	Placebo + Placebo	371 ±46	337 ±54	351 ±48	320 ±40	329 ±34	365 ±44

† $p<0.05$ vs Indomethacin
* $p<0.05$ vs Placebo
** $p<0.02$ vs Placebo
*** $p<0.01$ vs Placebo

TABLE II. Urinary 6-keto-$PGF_{1\alpha}$ excretion in pmol/min. Values expressed as Mean ± SEM

Group \ Time	Control	90 min	150 min
Felodipine + Placebo	1341 ±130	1393* ±102	1239* ± 97
Felodipine +Indomethacin	890 ±157	819 ±106	683 ±58
Placebo + Placebo	1078 ±174	792 ±127	894 ±120

* $p<0.01$ vs Indomethacin

Discussion

This study of the acute administration of Felodipine in normal men has demonstrated marked natriuretic and diuretic properties of the drug which seem to occur in two phases, the increase in urine volume and free water clearance preceding an increase in sodium excretion. One possible mediator of this response is an increase in renal plasma flow, although with other arteriolar vasodilators such as Hydralazine, such an increase is not associated with natriuresis [6]. Despite the

limitations of clearance techniques they remain the most accurate methods of assessing renal plasma flow and glomerular filtration rate in humans. This study has shown no effect of Felodipine on either of these parameters, using a dose that has a significant hypotensive effect when given as a first dose in the therapy of hypertension.

The response to Felodipine seems likely to be due to a reduction in tubular reabsorption of sodium and water. This hypothesis is supported by a recent micropuncture study by Dibona et al [7], who looked at the action of Felodipine on tubular sodium and water excretion. They found no change in proximal tubular or early distal tubular sodium excretion but a reduction in sodium reabsorption occurred in the latter half of the distal tubule and the collecting ducts; water reabsorption was decreased in the collecting ducts.

Prostaglandins are important modulators of renal function, particularly in response to stress, the two principal prostaglandins synthesized in the kidney are PGI_2 and PGE_2. When infused into the kidney both have powerful vasodilator and natriuretic properties, PGE_2 is also an antagonist of the action of vasopressin on water transport in the collecting duct. 6-keto-$PGF_1\alpha$ is the stable metabolite of PGI_2 excreted in urine. Indomethacin is a potent inhibitor of renal prostaglandin synthesis.

The study of Felodipine in the presence of Indomethacin demonstrated that whereas there is no significant effect of inhibition of prostaglandin synthesis on the natriuresis the water diuresis is delayed. This can be interpreted as evidence for a dual action of Felodipine. It is possible that the initial diuresis is a result of a direct action on the collecting duct by Felodipine, perhaps by antagonizing the cellular response to vasopressin by inhibiting calcium mobilization. A study of the effects of the calcium antagonists Verapamil and Proadifen demonstrated that the response to infused vasopressin in Indomethacin-treated dogs was attenuated by these drugs suggest a direct blocking action of the anti-diuretic response to vasopressin by calcium inhibition [8]. The delay in diuresis following Indomethacin in our study may mean that the dose of Felodipine was insufficient to overcome the increased sensitivity of collecting ducts to circulating vasopressin where prostaglandin synthesis was inhibited. Felodipine, by inhibiting sodium reabsorption in the distal tubule, will increase sodium delivery to the collecting duct and thus a second phase of diuresis will follow.

It remains to be established whether Felodipine has an equally potent natriuretic action in hypertensive patients as in normal men; it was however noted in a crossover study with Minoxidil [5] that a fall in weight occurred in patients after switching to Felodipine. This suggests that the natriuresis is also sustained in hypertensives. The precise mode of action on the kidney remains unclear but we have not found evidence to suggest that it is mediated by effects on prostaglandin synthesis, nor by increasing renal plasma flow, and indeed the dominant effect appears most likely to be due to a direct effect on tubular sodium reabsorption.

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