The effect of enalapril on the renal response to tilting in humans

N. P. LEWIS & D. R. FERGUSON

Department of Pharmacology, University of Cambridge, Hills Road, Cambridge

1 Seventeen normal subjects were tilted on a tilt table and changes in blood pressure, heart rate and renal function were monitored in the absence of drug treatment; the same measurements were repeated during treatment with enalapril in eight of these subjects.

2 In the absence of drug, tilting of the whole body to the 45° head up position caused an antidiuresis, antinatriuresis and antikaliuresis; the antinatriuresis resulted from a transient fall in glomerular filtration and from a sustained increase in the tubular reabsorption of sodium, as reflected by a prolonged fall in fractional sodium excretion.

3 Enalapril caused a reduction in blood pressure in the upright position; there was no effect on heart rate. The antinatriuresis of tilt was significantly blunted by enalapril. This resulted from blunting of the transient fall in creatinine clearance and of the increase in tubular sodium reabsorption. Urinary potassium excretion during tilting was not altered by enalapril.

4 These findings are consistent with a direct intrarenal action of angiotensin II, mediating some of the alterations in renal function apparent on assumption of the upright position.

Keywords renin angiotensin system posture renal function enalapril

Introduction

Studies performed in animals suggest that angiotensin II has direct actions which alter renal function. Angiotensin II receptors have been identified in glomeruli (Sraer *et al.*, 1974) and in renal tubules (Brown & Douglas, 1982, 1983; Cox *et al.*, 1984). Infusion of angiotensin II into the renal artery has been shown to cause a fall in RBF and in GFR, and a reduction in the urinary excretion of electrolytes and water (Navar & Langford, 1974). In animals maintained on a low sodium intake, the administration of teprotide or captopril to inhibit angiotensin II formation (Kimbrough *et al.*, 1977), or saralasin to block angiotensin II receptors, causes an increase in RBF, GFR and electrolyte and water excretion (Trippodo *et al.*, 1971), where the fall in systemic blood pressure is small. Direct intrarenal action of angiotensin II in humans has been suggested by the effect of captopril on renal function in normal and hypertensive subjects fed a low sodium diet (Hollenberg *et al.*, 1977, 1979), and by the renal effects of a subpressor infusion

of angiotensin II given into a peripheral vein (Dusing *et al.*, 1985).

In normal humans, transfer from the recumbent to the upright position is associated with a twofold rise in plasma renin activity (Oparil *et al.*, 1970), an antidiuresis, antinatriuresis and antikaliuresis (Pearce & Newman, 1954; Streeten & Speller, 1966; Surshin & White, 1956). To assess the degree to which the renin angiotensin system causes changes in renal function when body posture changes, we have examined the effects of the angiotensin converting enzyme inhibitor enalapril on renal functional changes seen after tilting the whole body.

Methods

Subjects

Seventeen normal volunteers (mean age 34 years, range 22–62 years; three female) were studied

Correspondence: Dr N. P. Lewis, Department of Cardiology, University Hospital of Wales, Cardiff CF4 4XW

with informed consent. The experimental protocol was approved by the ethics committee of Addenbrooke's Hospital, Cambridge. Control experiments were carried out on all 17 subjects; the experiment was repeated in eight subjects (mean age 33 years, range 26–50 years; all male) after treatment with enalapril 5 mg orally 1 h prior to the experiment. Enalapril inhibits converting enzyme; inhibition is maximal 4 h after oral dosing, and most of this effect is present within 1 h of oral dosing (Brunner *et al.*, 1985). The remaining nine subjects were restudied after treatment with a β -adrenoceptor blocker. These two subsets were similar with respect to their age, blood pressure and renal responses to tilting in the absence of drug and selection into the two subsets was randomised.

Protocol

Pre- and post-drug studies were carried out in each subject at the same time on consecutive days. The day on which the drug was given was randomised. Subjects were asked to observe a similar dietary intake for 2 days prior to the study, and for the 2 days of the study; no attempt was made to feed the same diet to all subjects. Alcohol, tea and coffee and smoking were prohibited on the days of the experiments.

Prior to the experiment, subjects emptied their bladder. Tap water 100 ml h^{-1} was given to drink throughout the experiment. Subjects were placed in the 30° head down position on a tilting table for 120 min and voided immediately after tilt to the 45° head up position. Urine was subsequently voided in this position at 30 min intervals for a further 120 min. Urine volumes were measured from each voiding period, and an aliquot taken for measurement of sodium, potassium and creatinine. Blood pressure was measured using a mercury random zero sphygmomanometer; heart rate was measured by counting the pulse for 1 min; these values were recorded after 60, 120 and 180 min. Blood samples were taken for measurement of sodium, potassium and creatinine at the mid-points of each clearance period. From these data, urine flow, total and fractional sodium excretion, potassium excretion and creatinine clearance were calculated.

Biochemical measurements

Urine and plasma sodium and potassium were measured by flame photometry, and creatinine by the manual alkaline picrate method.

Analysis of results

To standardise the results from different individuals, which varied due to differences in dietary

electrolyte intake, control and post-drug comparisons were made after expressing all measurements as a percentage of the respective value obtained during the 30° head down position for each subject. Statistical analysis of results was carried out by analysis of variance for repeated measures. Where a significant result was obtained overall, the differences between individual means were compared by *t*-test. $P < 0.05$ was taken as significant.

Results

Renal effects of tilting

Tilting from the 30° head-down to the 45° head-up position was associated with a significant fall in urine flow to approximately 25% of the value

Figure 1 The effect of tilting on mean blood pressure and heart rate. The upper panel shows the changes in blood pressure (histogram) and heart rate in all 17 subjects examined in the absence of drug. The lower panel shows the changes in heart rate and blood pressure in the subset of eight subjects examined before and after enalapril. Results after enalapril are represented by the unhatched histogram, and by the square points. Values shown are means and s.e. mean, * $P < 0.005$.

in the head-down position after 60 min of tilt (Figure 2); there was no significant change in mean arterial pressure or in pulse rate (Figure 1). Tilting caused a fall in urinary sodium excretion to approximately 50% of the head-down value (Figure 3), and there was a similar reduction in urinary potassium excretion (Figure 4).

Creatinine clearance was reduced by tilting to about 70% of the head-down value after 60 min. Over the final 60 min of observation creatinine clearance increased again toward the value observed in the head-down period (Figure 5). After 120 min in the head-up position, creatinine clearance was not significantly different from the value measured in the head-down position.

Figure 2 The effect of tilting on urine flow. The upper panel shows the changes in urine flow in all 17 subjects examined in the absence of drug. The lower panel shows the changes in urine flow in the subset of eight subjects examined before and after enalapril. Results after enalapril treatment are represented by the open circles. Values shown are means and s.e. mean. *** $P < 0.001$.

Figure 3 The effect of tilting on urinary sodium excretion. The upper panel shows the changes in urinary sodium excretion in all 17 subjects examined in the absence of drug. The lower panel shows the changes in urinary sodium excretion in the subset of eight subjects examined before and after enalapril. Results after enalapril treatment are represented by the open circles. Values shown are means and s.e. mean. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Fractional sodium excretion showed a sustained fall on tilting, indicating a sustained increase in tubular sodium reabsorption (Figure 6).

Reproducibility of the renal effects of tilting

In five further subjects tilting was performed on consecutive days to assess the reproducibility of the renal response to tilting. The findings are shown in Table 1, demonstrating that the renal response to tilt was consistent using the protocol above.

Figure 4 The effect of tilting on urinary potassium excretion. The upper panel shows the changes in urinary potassium excretion in all 17 subjects examined in the absence of drug. The lower panel shows the changes in urinary potassium excretion in the subset of eight subjects examined before and after enalapril. Results after enalapril treatment are represented by the open circles. Values shown are means and s.e. mean. *** $P < 0.001$.

Effect of enalapril on the renal response to tilt

Enalapril reduced mean arterial blood pressure by 10 mmHg ($P < 0.05$) in the upright position; there was no change in heart rate (Figure 1). Urine flow rates during tilt were not significantly affected by treatment with enalapril (Figure 2). The fall in sodium excretion during tilting was significantly blunted by enalapril (Figure 3), but there was no significant effect on potassium excretion (Figure 4).

The transient fall in creatinine clearance and the fall in fractional sodium excretion were both significantly blunted by enalapril (Figures 5 and 6).

Figure 5 The effect of tilting on creatinine clearance. The upper panel shows the changes in creatinine clearance in all 17 subjects examined in the absence of drug. The lower panel shows the changes in creatinine clearance in the subset of eight subjects examined before and after enalapril. Results after enalapril treatment are represented by the open circles. Values shown are means and s.e. mean. * $P < 0.05$, ** $P < 0.01$.

Discussion

Preliminary assessment in five subjects suggested that under the conditions of the experiment, and in the absence of drug treatment, the renal response to tilting was consistent within an individual on consecutive days (Table 1).

The renal response to tilting described in these experiments agrees well with previous reports (Pearce & Newman, 1954; Streeten & Speller, 1966; Surshin & White, 1956) which describe an antidiuresis, antinatriuresis and antikaliuresis in

Figure 6 The effect of tilting on fractional sodium excretion. The upper panel shows the changes in fractional sodium excretion in all 17 subjects examined in the absence of drug. The lower panel shows the changes in fractional sodium excretion in the subset of eight subjects examined before and after enalapril. Results after enalapril treatment are represented by the open circles. Values shown are means and s.e. mean. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

response to the upright position. Previous studies have produced conflicting results regarding the contribution of altered GFR and tubular reabsorption to the antinatriuresis and antidiuresis of tilting (Edwards, 1974), possibly due to the different urine sampling periods employed. Examination of all the data presented shows no clear correlation between the postural change in sodium excretion and the change in GFR (Edwards, 1974), suggesting that changes in GFR alone do not wholly account for the altered electrolyte excretion. Our data demonstrate a transient fall in creatinine clearance and a sustained fall in fractional sodium excretion,

suggesting that the antinatriuresis of tilting results both from a transient fall in GFR and from a sustained increase in the tubular reabsorption of sodium.

The possibility that these alterations in renal function could result from incomplete bladder emptying should be considered. However, this seems unlikely as the changes in creatinine clearance and urine flow are dissociated during tilting (Figures 2 and 5).

A limitation of this study is that evidence of the inhibition of converting enzyme by enalapril during experiments is indirect, based on published data in normal subjects which demonstrates inhibition of converting enzyme by enalapril, at the dosage used, over the time course of these experiments (Brunner *et al.*, 1985). We found that enalapril significantly blunted postural antinatriuresis, by blunting the transient fall in GFR and the increase in tubular sodium reabsorption (Figures 3, 5 and 6). Enalapril had no significant effect on the urinary excretion of potassium during tilting.

Our results largely agree with a previous report (Mimran & Deschodt, 1983) which examined the effect of captopril on renal and hormonal function during whole body tilting; Mimran & Deschodt (1983) concluded that following inhibition of angiotensin II synthesis by captopril, the falls in GFR and sodium excretion on tilting were blunted but the fall in fractional sodium excretion was not affected; however, in their experiments, renal changes were observed over only 30 min of tilt. It can be seen from our results that the change in fractional sodium excretion had not reached a significant level after 30 min of tilt (Figure 6), and that any effect of converting enzyme inhibition on this parameter would become apparent only after long periods of observations during tilting.

Converting enzyme inhibitors may alter renal function via mechanisms other than the inhibition of angiotensin II synthesis. Kinin degradation by kininase II is also inhibited, although not consistently in sodium replete subjects (Mimran & Deschodt, 1983; Hollenberg *et al.*, 1981), raising the possibility that accumulation of kinins may be responsible for some of the alteration in renal function found in these experiments. Converting enzyme inhibitors also cause a rise in the production of the vasodilator prostaglandin E_2 (Swartz *et al.*, 1980) which may be implicated in some of the renal changes noted in our study. Angiotensin II is known to potentiate the effects of noradrenaline (Khairallah, 1972) and inhibition of angiotensin II synthesis by enalapril may affect renal function by modification of the effects of the sympathetic nervous system (Katholi,

Table 1 Urine flow, total urinary sodium and potassium excretion, creatinine clearance and fractional sodium excretion at 30 min intervals after tilting from the 30° head down to the 45° head up position in five subjects studied on consecutive days in the absence of drug treatment. All results are expressed as a percentage of the value obtained in the respective control period. Values shown are means (s.e. mean); no significant difference was noted between the 2 days

	Time (min) after tilting to head up position			
	30	60	90	120
<i>Urine flow (% control)</i>				
Day 1	62 (8.5)	27.7 (6.3)	20.2 (2.6)	17.2 (2)
Day 2	64.4 (12.1)	22.6 (2.7)	17 (2.5)	19.6 (2.2)
<i>Na excretion (% control)</i>				
Day 1	91.8 (7.8)	59.7 (9.3)	60.9 (10.5)	50.3 (10.2)
Day 2	89.6 (9)	51.7 (16.1)	59.9 (12.8)	55.2 (12.6)
<i>K excretion (% control)</i>				
Day 1	94.1 (10.9)	47.3 (7)	46.3 (7.6)	39.2 (7.5)
Day 2	92.5 (4.6)	50.6 (8.5)	43.7 (7.4)	44.3 (8.1)
<i>Creatinine clearance (% control)</i>				
Day 1	96 (11.3)	71.4 (4.4)	86 (8.3)	88.5 (7.5)
Day 2	89.7 (14)	75.5 (8.3)	81.3 (8.9)	93.6 (8)
<i>Fractional Na excretion (% control)</i>				
Day 1	101.6 (9.8)	84.3 (13.1)	78.4 (15.2)	61.2 (13.4)
Day 2	98.7 (12.1)	77.6 (10.6)	73.8 (11.3)	57.6 (15.2)

1983) at the kidney. A recent report has suggested that inhibition of converting enzyme with captopril is associated with an increase in resting plasma atrial natriuretic peptide levels (Wilkins *et al.*, 1987), raising the possibility that some of the renal effects demonstrated in our experiments may result from altered atrial peptide metabolism.

In summary, our data show that the postural change in urinary sodium excretion in normal humans is due to a transient reduction in GFR, and a sustained increase in tubular sodium reabsorption. The effects of enalapril on the postural change in renal function support the hypothesis that the antinatriuresis of the upright

position results in part from the direct action of angiotensin II at the glomerulus causing a transient fall in GFR, and in part from an increase in tubular sodium reabsorption. Whether the increase in tubular reabsorption is due to a direct effect of angiotensin II on tubular mechanisms (Harris & Young, 1977) or to altered peritubular forces (Levens *et al.*, 1981) cannot be determined from our results in the absence of direct measurements of renal blood flow. The time course of the change in tubular sodium reabsorption and the reduction in potassium excretion on tilting suggest that aldosterone is not the primary effector (Reid, 1984).

References

- Brown, G. P. & Douglas, J. G. (1982). Angiotensin II binding sites on isolated rat renal brush border membranes. *Endocrinology*, **111**, 1830–1836.
- Brown, G. P. & Douglas, J. G. (1983). Angiotensin II binding sites in rat and primate isolated renal tubular basolateral membranes. *Endocrinology*, **112**, 2007–2014.
- Brunner, H. R., Nussberger, J. & Waeber, B. (1985). The present molecules of converting enzyme inhibitors. *J. cardiovasc. Pharmac.*, **7**, S2–S11.
- Cox, H. M., Munday, K. A. & Poat, J. A. (1984). Location of ¹²⁵I-angiotensin II receptors on rat kidney cortex epithelial cells. *Br. J. Pharmac.*, **82**, 891–895.
- Dusing, R., Morik, J., Glanzer, K. & Kramer, H. J. (1985). Effects of angiotensin II and captopril on renal tubular function in man. *Br. J. clin. Pharmac.*, **19**, 29–35.
- Edwards, O. M. (1974). *Idiopathic oedema*. M.D. Thesis, University of London.

- Harris, P. J. & Young, J. A. (1977). Dose dependent stimulation and inhibition of proximal tubular sodium reabsorption by angiotensin II in the rat kidney. *Pflügers Arch.*, **367**, 295–297.
- Hollenberg, N. K., Meggs, L. G., Williams, G. H., Garnic, J., Garnic, J. D. & Harrington, D. P. (1981). Sodium intake and renal responses to captopril in normal man and in essential hypertension. *Kidney Int.*, **20**, 240–245.
- Hollenberg, N. K., Swatz, S. L. & Passan, D. R. (1979). Increased GFR following converting enzyme inhibition in essential hypertension. *New Engl. J. Med.*, **301**, 9–12.
- Hollenberg, N. K., Williams, G. H. & Taub, K. J. (1977). Renal vascular response to interruption of the renin angiotensin system in normal man. *Kidney Int.*, **12**, 285–293.
- Katholi, R. E. (1983). Renal nerves in the pathogenesis of hypertension in experimental animals and humans. *Am. J. Physiol.*, **245**, F1–F14.
- Khairallah, P. A. (1972). Action of angiotensin on adrenergic nerve endings: inhibition of norepinephrine uptake. *Fed. Proc.*, **31**, 1351–1357.
- Kimbrough, H. M. Jnr., Vaughan, E. D. Jnr., Carey, R. M. & Ayers, C. R. (1977). Effect of intrarenal angiotensin II blockade on renal function in conscious dogs. *Circ. Res.*, **40**, 174–178.
- Levens, N. R., Peach, M. J. & Carey, R. M. (1981). Role of the intrarenal renin angiotensin system in control of renal function. *Circ. Res.*, **48**, 157–167.
- Mimran, A. & Deschodt, G. (1983). The role of the renin angiotensin system in the hormonal and renal responses to tilt in normal man. *Renal Physiol.*, **6**, 36–42.
- Navar, L. G. & Langford, H. G. (1974). In *Angiotensin*, eds Page, I. H. & Bumpus, F. H., pp. 455–474. New York: Springer Verlag.
- Oparil, S., Vassaux, C., Sanders, C. A. & Haber, E. (1970). Role of renin in acute postural homeostasis. *Circulation*, **41**, 89–95.
- Pearce, M. L. & Newman, E. V. (1954). Some postural adjustments of salt and water excretion. *J. clin. Invest.*, **33**, 1089–1094.
- Reid, I. A. (1984). In *Edema*, eds Staub, N. C. & Taylor, A. E., pp. 353–370. New York: Raven Press.
- Sraer, J. D., Sraer, J., Ardaillou, T. & Mimourne, O. (1974). Evidence for renal glomerular receptors for angiotensin II. *Kidney Int.*, **6**, 241–246.
- Streeten, D. H. & Speller, P. J. (1986). The role of aldosterone and ADH in the postural changes in renal excretion in normal subjects and in patients with idiopathic oedema. *Metabolism*, **15**, 53–64.
- Surshin, A. & White, H. L. (1956). Postural effects on renal tubular activity. *J. clin. Invest.*, **35**, 267–271.
- Swartz, S. L., Williams, G. H., Hollenberg, N. K., Levine, L., Dluhy, R. G. & Moore, T. J. (1980). Captopril induced changes in prostaglandin production. Relationship to vascular responses in normal man. *J. clin. Invest.*, **65**, 1257–1264.
- Trippodo, N. L., Hall, J. E., Lohmeier, T. E. & Guyton, A. C. (1971). Intrarenal role of angiotensin II in controlling sodium excretion during dehydration in dogs. *Clin. Sci. mol. Med.*, **52**, 454–458.
- Wilkins, M. R., Lewis, H. M., West, M. J. & Lote, C. J. (1987). Captopril reduces the renal response to intravenous atrial natriuretic peptide in normotensives. *J. Human Hypertension*, **1**, 47–51.

(Received 16 June 1988,
accepted 12 October 1988)