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Effect of Indapamide on Renal Plasma Flow, Glomerular Filtration Rate and Arginine Vasopressin in Plasma in Essential Hypertension

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Summary. Renal plasma flow (RPF), glomerular filtration rate (GFR), arginine vasopressin in plasma (AVP), free water clearance (C_{H_2O}) and blood pressure (BP) were determined in 11 patients with essential hypertension at the end of 3 consecutive periods of observation each of 6 of weeks duration; indapamide 2.5 mg daily was given in period 2 and placebo in periods 1 and 3. RPF and GFR were reduced by 9% and BP by 9%/14% supine and 14%/12% standing during indapamide treatment. Changes in renal haemodynamics were not correlated with those in BP. AVP was not significantly altered by indapamide and was not correlated with BP. Indapamide reduced C_{H_2O} possibly due to the reduction in GFR. It is concluded that indapamide evidently induces redistribution of the cardiac output, with enhanced muscle blood flow and reduced renal perfussion, and that AVP does not seem to be involved in blood pressure regulation in mild to moderate essential hypertension under basal conditions.

Key words: indapamide, hypertension; glomerular filtration, arginine vasopressin, free water clearance, blood pressure

The antihypertensive effect of indapamide is well documented (Schlesinger et al. 1977; Campbell and Moore 1981), but its effect on renal haemodynamics in humans has not been studied to any degree. In animal experiments, renal plasma flow (RPF) and glomerular filtration rate (GFR) were unchanged after intravenous administration of indapamide (Laubie and Schmitt 1977), and in 6 healthy control subjects, RPF and GFR were unaffected by a single oral dose (Onesti et al. 1977). However, there do not appear to be any studies available of the long-term effect of indapamide on renal haemodynamics in essential hypertension.

The importance of vasopressin in blood pressure regulation is not clear (Möhring et al. 1977; Bartter 1981; Johnston et al. 1981; Share and Crofton 1982). The plasma concentration of arginine vasopressin (AVP) was reduced during antihypertensive treatment with captopril, and it has been suggested the fall in AVP might be a mechanism for lowering the blood pressure (Thibonnier et al. 1981). The effect of indapamide on AVP is unknown.

The purpose of the present investigation was to study the effect of indapamide in mild to moderate essential hypertension on 1. RPF and GFR, 2. AVP, 3. free water clearance C_{H_2O}, 4. blood pressure (BP), and 5. on the relationship between the changes in renal haemodynamics and AVP on the one hand and the reduction in BP on the other.

Material and Methods

Patients

Eleven patients with essential hypertension, 10 males and 1 female, mean age 39 years (range 23–58 years) were studied. Their mean blood pressure was 163/113 mmHg (range 145–180/105–118) on admission. Hypertension due to aortic coarctation or to disease of the kidneys, renal arteries or suprarenal glands was excluded by physical examination, measurement of serum electrolytes and creatinine, culture and screening of urine for protein and microscopy, renography and measurement of urinary excretion of adrenaline, noradrenaline and vanillylmandelic acid. Hypertensive retinal lesions were Grade I (Keith-Wagner) in 3 patients and Grade II in 4; 4 patients had no retinal lesion. None had electrocardiographic signs of left ventricular hypertrophy and the cardio-thoracic ratio was normal in all but 1 patient. 5 patients had previously been treated with antihypertensive agents. All therapy was discontinued 6 weeks before the study.

Informed consent from all patients was obtained in accordance with regulations of the local medical ethics committee.

Procedure

The studies were performed in 3 consecutive 6-week periods. Placebo was given in Periods 1 and 3, and active therapy with indapamide (Fludex®) 2.5 mg daily was given in Period 2. RPF and GFR were determined at the end of each of the three periods. AVP was determined at the end of each period, at 9.00 a.m. after a 1 h rest in the supine position following a fast for 8 h. C_{H_2O} was determined during the clearance periods, and AVP was measured at the end of the clearance periods. BP and pulse rate (PR) were determined in the supine and standing position, in the middle and at the end of each period. BP and PR were measured 3 times in both positions on each occasion and the average values were used.

Methods

GFR and RPF were measured using a constant infusion technique. The reference substances employed were ^{131}I-hippuran and ^{125}iothalamate (Amersham Radiochemical Pharmaceuticals). A priming dose ensured plasma activity of 200–600 cpm/ml for ^{131}I-hippuran and 800–1600 cpm/ml for ^{125}iothalamate. Plasma activity was kept stable by constant infusion with a Holter infusion pump. Patients voided in either the standing or the sitting position; bladder catheterization was not performed. Over 1 h immediately prior to examination, 1000 ml water was given to each patient, followed by a further 500 ml/h during the actual clearance periods. 4 clearance periods, each of 30 min duration, were studied at each examination. Earlier investigations (Mogensen 1971; Skov and Hansen 1974) had shown that ^{131}I-hippuran and ^{125}iothalamate were reliable substances for measurement of RPF and GFR.

Blood samples for determination of arginine-vasopressin (AVP) were collected in cooled, heparinized plastic tubes and were centrifuged immediatedly at 4 °C. AVP was measured by radioimmunoassay after extraction of plasma. The extraction was performed in cooled glass vials; 1 ml plasma was mixed with 2 ml cold acetone to precipitate plasma proteins. After centrifugation, 4 ml cold petroleum ether was added to the supernatant to extract lipids. The mixture was centrifuged, the top petroleum ether phase was removed and the remaining acetone phase was dried under a stream of air. The extracted plasma was stored frozen until assayed. AVP standards were prepared in phosphate buffer and the unknown extracted test samples were redissolved in phosphate buffer. Two phase incubation was used and separation performed by the double-antibody technique. Synthetic AVP purchased from Ferring AB (Malmö, Sweden) was used for preparation of standards and iodination. Iodination was performed by the chloramine T method. AVP antibody produced in rabbits was purchased from Hoechst. Sheep antirabbit gammaglobulin was obtained from Statens Seruminstitut, Denmark. The method is a modification of a previously published radioimmunoassay (Robertson et al. 1973). The coefficient of variation (interassay) was 12%.

The osmolar concentration of serum (S_{osm}) and urine (U_{osm}) was determined with a 65-31 Advanced Osmometer. C_{H_2O} was determined by substracting osmolar clearance (C_{osm}) from urine flow (V). C_{osm} was calculated according to the formula $C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$

BP was measured with a Hawksley Random Zero Sphygmomanometer. The Phase V disappearance of the Korotkoff sounds was taken as the diastolic blood pressure.

Non-parametric tests were used for the statistical analysis (Bradley 1968). Wilcoxon's signed rank test was used for paired comparisons between two groups, and correlations were calculated by Spearman's test.

Results

Renal Plasma Flow and Glomerular Filtration Rate

RPF, GFR and filtration fraction (FF) are shown in Table 1. RPF was significantly lower during indapamide treatment (mean 368 ml/min) than at the end of both the first (414 ml/min, $p < 0.01$) and the second (397 ml/min, $p < 0.01$) placebo period. GFR changed in the same way, i.e. the level during indapamide (96 ml/min) was significantly lower than in both the first (106 ml/min, $p < 0.01$) and second (104 ml/min, $p < 0.01$) placebo period. The reduction both for RPF and GFR was 9% of the average level in the two placebo periods. FF did not change significantly during indapamide therapy. There was no significant correlation between changes in RPF or GFR and the changes either in systolic or diastolic BP.

Arginine-Vasopressin

Basal AVP level was the same after indapamide treatment (2.2 pg/ml, range 1.2–3.8) as after both the first – (2.1 pg/ml, range 0.5–3.4) and the second (2.3 pg/ml, range 1.1–3.9) placebo periods. There

Table 1. Renal plasma flow (RPF), glomerular filtration rate (GFR) and filtration fraction (FF) in 11 patients with essential hypertension at the end of two placebo periods (P) and one period of indapamide treatment (I)

Patient No	RPF [ml/min]			GFR [ml/min]			FF		
	P	I	P	P	I	P	P	I	P
1	411	313	410	103	90	101	0.251	0.288	0.246
2	330	289	355	101	95	101	0.306	0.329	0.285
3	425	375	362	106	92	105	0.249	0.245	0.290
4	410	357	372	118	101	107	0.288	0.283	0.288
5	541	480	540	132	118	133	0.244	0.246	0.246
6	256	236	257	66	56	69	0.258	0.237	0.268
7	443	397	384	103	95	99	0.233	0.239	0.258
8	567	459	473	126	108	114	0.222	0.235	0.241
9	340	369	378	98	99	103	0.288	0.268	0.272
10	445	402	420	104	93	100	0.234	0.231	0.238
11	391	375	421	107	104	115	0.274	0.277	0.273
Mean ±SD	414 89	368 71	397 72	106 17	96 15	104 15	0.259 0.027	0.262 0.030	0.264 0.019

was no significant correlation between AVP and either systolic or diastolic BP. There was no significant difference in S_{osm} between Period 1 (287 mosmol/kg, range 281–294), Period 2 (287 mosmol/kg, range 278–292) and Period 3 (289 mosmol/kg, range 286–293).

Free Water Clearance

In 9 patients C_{H_2O} was determined during the clearance tests in each of the three periods studied. The average C_{H_2O} was significantly lower after indapamide therapy (4.1 ml/min, range 1.9–6.0) than after the first – (6.5 ml/min, range 3.8–10.2, $p<0.05$) or second (6.4 ml/min, range 1.5–9.6, $p<0.02$) placebo periods.

AVP was determined at the end of the clearance periods. The lowest level during each of the three examinations was significantly reduced when compared to the initial basal level (first placebo period 2.1 pg/ml (range 0.5–3.4) to 1.0 pg/ml (0.5–2.1), $p<0.01$; indapamide period 2.1 pg/ml (1.2–3.8) to 1.4 pg/ml (0.5–3.2), $p<0.01$; second placebo period 2.1 pg/ml (1.1–3.9) to 1.3 pg/ml (0.5–2.5), $p<0.01$). The average reduction in AVP during the clearance tests was the same in both the placebo and indapamide periods.

Blood Pressure and Pulse Rate

BP levels are shown in Fig. 1. During indapamide treatment the systolic and diastolic BPs were significantly lower in both the supine and standing positions than at the end of the two placebo periods. At the end of indapamide treatment, the BP reduction was supine 8%/11% ($p<0.02/p<0.01$) and standing 14%/12% ($p<0.01/p<0.01$) when compared to the end of the first placebo period, and supine 9%/14% ($p<0.01/p<0.01$) and standing 14%/12% ($p<0.01/p<0.01$) when compared to the second placebo period.

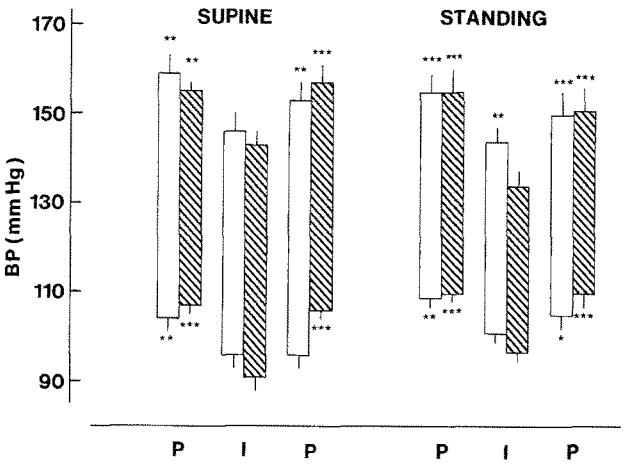

Fig. 1. Blood pressure (BP) in 11 patients with essential hypertension, supine and standing, at the middle (*white columns*) and the end (*dotted columns*) of each of the three 6 week periods

P = placebo treatment and I = indapamide treatment. Significance of change in blood pressure level at the end of indapamide treatment: *** = $P<0.01$, ** = $p<0.02$, * = $p<0.05$. Mean ± SEM

The supine diastolic BP did not change significantly from the end of the indapamide period to the middle of the second placebo period, whereas the supine systolic and standing systolic and diastolic BPs increased significantly (supine: $p<0.02$/n.s.; standing: $p<0.01/p<0.05$). However, at the end of the second placebo period both the supine and standing BPs were the same as in the first placebo period.

Table 2. Pulse rate (beats/min), supine and standing, in 11 patients with essential hypertension at the middle (3 weeks) and the end (6 weeks) of two placebo periods (P) and one period of indapamide treatment (I)

	P		I		P	
	3 weeks	6 weeks	3 weeks	6 weeks	3 weeks	6 weeks
Supine						
Mean	75	75	77	73	74	70
±SD	12	10	10	9	8	10
Standing						
Mean	86	83	95	90	87	83
±SD	12	12	13	9	10	12
Significance	$p<0.01$	$p<0.01$	$p<0.01$	$p<0.01$	$p<0.01$	$p<0.01$

PR in the middles and at the end of the 3 test periods is shown in Table 2. There was no significant change in the supine position. In the standing position, however, PR tended to be elevated during indapamide, but there was considerable variation and significant differences were only found when the level at the end of the second placebo period was compared with that at the middle ($p<0.01$) and the end ($p<0.05$) of the indapamide period. PR increased significantly from the supine to the standing position in all periods ($p<0.01$).

Discussion

The present results showed that indapamide reduced RPF and GFR approximately 9% in mild to moderate essential hypertension.

No other studies are available about the effect of indapamide on renal haemodynamics in essential hypertension. The biochemically related thiazides do not significantly change RPF or GFR after one month of therapy (Warren et al. 1981). Alterations in renal haemodynamics during antihypertensive treatment have been considered secondary to changes in the extracellular volume or cardiac output (Pedersen 1978; Pedersen 1979; Epstein and Oster 1982). Blood volume, plasma volume and exchangeable sodium were unchanged during indapamide therapy (Isaac et al. 1977; Weidmann et al. 1980), and the drug has no or only a minimal diuretic effect in the dose of 2.5 mg/day (Onesti et al. 1977; Schlesinger et al. 1977). Cardiac output was slightly increased (Dunn et al. 1981) or unchanged (Horgan et al. 1981) using non-invasive cardio-vascular assessment. However, in most previous studies (Campbell and Moore 1981), and in the present report, PR has remained at the same level before and after indapamide therapy. Accordingly, the indapamide-induced reduction in RPF and GFR cannot be a secondary phenomenon due to a smaller extracellular volume or a lower cardiac output.

The mechanism responsible for the blood pressure lowering effect of indapamide is a decrease in the total peripheral resistance. Animal experiments suggest that this could be attributed to a decrease in reactivity to circulating pressor substances, i.e. noradrenaline, angiotensin II and vasopressin (Finch et al. 1977; Uhlich et al. 1977), and, correction of abnormally high noradrenaline reactivity in essential hypertension has recently been demonstrated (Grim et al. 1981). According to the results of Burgess et al. (1981), the reduction in the peripheral resistance is most pronounced in the muscles, since resting muscle blood flow increased by 53% after 6 weeks of treatment with indapamide. In the present study a change in renal haemodynamics was also demonstrated after 6 weeks. Evidently, indapamide induces a redistribution of cardiac output, with enhanced muscle blood flow and reduced kidney perfussion. The reasons for these alterations in blood flow are not known, but may be due to differences in the effect of indapamide in different vascular areas.

Blood pressure was significantly reduced by indapamide both in the supine and standing positions, and there was no important orthostatic decrease. The supine diastolic blood pressure remained reduced 3 weeks after cessation of indapamide administration, but it had returned to the same level 6 weeks after treatment as during the first placebo period. These results are in good agreement with previous studies (Campbell and Moore 1981). Changes in blood pressure were not correlated with changes either in RPF or GFR during indapamide therapy. Thus, the possibility that the change in renal haemodynamics was simply a consequences of lower blood pressure, can be ruled out.

Vasopressin may be involved in blood pressure regulation due both to vasoconstriction and to its antidiuretic effect with subsequent expansion of the extracellular fluid volume. In mild to moderate essential hypertension AVP has been found to be increased in urine (Khokhar and Slater 1976) and plasma (Cowley et al. 1981), although normal plasma levels have been reported by others (Padfield et al. 1976; Thibonnier et al. 1981). In the present study the basal AVP level was normal, and there was no

significant correlation between AVP and either systolic or diastolic blood pressure. Indapamide therapy did not change AVP significantly, and there was no relationship between blood pressure reduction and AVP. Thus, according to our results, AVP does not appear to be involved in blood pressure regulation in essential hypertension under basal circumstances.

In good agreement with previous acute experiments (Laubie and Schmitt 1977; Onesti et al. 1977) C_{H_2O} was decreased by indapamide. The reduction in AVP during the clearance periods could be attributed to the oral water load. However, AVP was not reduced more in the indapamide period than in the placebo periods; and so the decrease in C_{H_2O} could not be related to differences in AVP. The lower C_{H_2O} during indapamide treatment could be due to the reduction in GFR or to a direct effect on the cortical diluting segment.

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