Similar effects of hydrochlorothiazide and spironolactone on plasma renin activity in essential hypertension

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Thiazide diuretics are the most frequently used antihypertensive drugs. They reduce arterial pressure when used alone and enhance the effectiveness of nondiuretic antihypertensive drugs when used in combination. They cause sustained reductions of plasma volume (PV) and elevate plasma renin activity (PRA).[1] Spironolactone, an aldosterone antagonist, produces similar effects on arterial pressure,[2, 3] plasma volume,[4] and plasma renin.[5, 6] Of the possible causes of this hyperreninemia, chronic oligemia seemed most likely to play a major role, because we had found an inverse relationship between PV and PRA in normal men, in men with untreated essential hypertension, and in patients with untreated renovascular hypertension.[7] However, treatment could bring other factors into play, such as decreases in arterial pressure,[8, 9] decreases of plasma sodium,[10] and modification of plasma potassium concentration.[11, 12] In addition, the possibility of a direct effect of these drugs on the juxtaglomerular apparatus should be considered, because renin release evoked by furosemide has been attributed partly to inhibition of sodium

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transport by macula densa cells.[13] Such a mechanism is not so readily accepted in explanation for elevation of PRA produced by spironolactone, because this drug is a potassium-sparing agent,[14] and may have its major renal effects on tubular cells distal to the macula densa, although there is evidence to suggest that it also affects proximal portions of the nephron.[15]

A group of hypertensive patients treated with hydrochlorothiazide alone and another treated only with spironolactone provided an opportunity to study the effects of these two diuretics on PRA in regard to changes in arterial pressure, plasma volume, and plasma sodium and potassium concentrations.

Methods

Twenty-four patients with essential hypertension were studied. Ten received hydrochlorothiazide, 12 spironolactone, and two received separate courses of each drug. The two groups were fairly equally matched in age; those treated with hydrochlorothiazide were between 30 and 63 years and those treated with spironolactone were between 35 and 63 years; in both groups most patients were between 45 and 55 years of age.

Patients with essential hypertension were selected because renal arterial or parenchymal diseases and primary aldosteronism add factors which could make the assessment of diuretic-induced changes difficult. All patients had been investigated for known causes of hypertension by intravenous urography and renal arteriography, and by measurement of urinary excretion rates of aldosterone and catecholamines whenever indicated by clinical features or laboratory findings. The severity of hypertensive vascular disease had been determined by tests of renal excretory function, electrocardiography, radiographic measurement of heart size, and grading of retinal arteriolar disease. Patients were either untreated or had been without antihypertensive drugs for a month or longer before control measurements.

All patients measured brachial arterial pressures at home twice daily, and weekly averages of supine readings were used to establish pretreatment levels and to assess results of therapy. When arterial pressure had stabilized, treatment was begun. Hydrochlorothiazide was usually given as 25 mg twice daily and spironolactone, 25 mg four times daily. In the former group, treatment ranged from 1 to 36 months with 8 of the 13 patients receiving treatment for 4 months or longer. The 14 patients given spironolactone were treated for periods of 1 to 12 months, and 8 of the 14 received the drug 3 or more months before the observations reported here were made.

Plasma volume, plasma renin activity, and serum sodium and potassium concentrations were measured before treatment and several times during treatment. The last results obtained, representing effects of the longest term of treatment, were used for this analysis. All measurements were made in the morning after supine rest for 30 to 45 minutes from blood samples obtained without stasis. Plasma volume was calculated from the volume of distribution of 2.5 μc of ^{125}I or 5 μc of ^{131}I human serum albumin, as previously reported.[16] Plasma renin activity was estimated using a modified Pickens method[7, 17] and expressed as nano-

grams of angiotensin/ml/4 hr of incubation. Serum sodium and potassium concentrations were measured by lithium internal standard flame photometry.

Statistical analyses were performed using conventional methods for calculating the significance of standard *t* tests and correlation coefficients.[18]

Results

Before treatment there were no significant differences between the two groups in regard to arterial pressure, plasma volume, plasma renin activity, and serum sodium and potassium concentrations (*Table 1*). With the exception of arterial pressure, mean values for each group were within normal ranges. Use of averages, however, obscures the heterogeneity within the groups, particularly in regard to plasma volume and plasma renin activity. For plasma volume our normal value for men is 18.7 ml/cm of height with a range from 14.7 to 22 ml/cm—representing the mean ± two standard deviations; for women, the mean is 15.3 ml/cm and range, 11.9 to 18.7 ml/cm.[15] Thus, with the exception of three patients (Nos. 1, 10, and 17), plasma volume was normal, but characteristic of essential hypertensives,[19] some had values in the lower part of the normal range and some in the upper. In regard to plasma renin activity, although the mean values were not significantly different from our previous findings in hypertensive patients,[7] in 8 of the 9 women and 11 of the 15 men PRA was less in essential hypertension than the previously reported means. Also in contrast to that earlier experience, no correlation was found between PV and PRA.

Serum potassium concentration was 3.5 mEq/liter or higher except in the one instance of 3.3 mEq/liter (No. 24). The concurrent finding of low plasma renin activity suggested the possibility of primary aldosteronism, but the reduced plasma volume was against this possibility and subsequently, urinary aldosterone was found to be normal.

Treatment with hydrochlorothiazide or spironolactone produced significant effects. In both groups arterial pressure, plasma volume, and serum sodium were similarly reduced and plasma renin activity was similarly elevated ($p < .001$ for a comparison of each measurement with its control value). Only in regard to serum potassium were the effects produced by the two diuretics different, with hydrochlorothiazide treatment reducing its concentration and spironolactone elevating it.

As for control data, group means during treatment obscured variations in responses. Whereas, without exception, plasma renin activity was elevated and, with only one exception (No. 2, spironolactone treatment), serum sodium concentration was reduced. Not all patients had a significant lowering of arterial pressure and in five, (Nos. 1, 3, 7, 20 and 22), plasma volume changed less than 1.0 ml/cm.

To assess the relative importance of these changes in plasma volume, serum sodium concentrations and arterial blood pressure as determinants of renin activity elevations, correlation coefficients (r) were calculated (*Table 2*). No relationship was found between percentile decreases of arterial pressure and increases of plasma renin. In regard to plasma volume, when data

Table 1.—Effects of hydrochlorothiazide and spironolactone treatment in patients with essential hypertension

Patient No.	Age, yrs	Sex	Arterial BP mm Hg		Plasma volume ml/cm		Renin activity ng/ml		Serum Na mEq/L		Serum K mEq/L	
			C	D	C	D	C	D	C	D	C	D
A. Hydrochlorothiazide treatment												
1	44	M	149/110	133/94	22.7	22.1	0.4	3.1	140	137	3.5	2.9
2	35	F	184/126	180/120	15.4	13.1	1.3	6.5	141	139	4.3	4.1
3	57	M	160/110	162/92	19.7	19.0	0.2	1.1	142	137	4.1	3.3
4	41	F	217/132	142/108	15.4	14.0	0.7	2.1	140	135	4.0	3.7
5	50	M	165/88	121/82	19.0	15.4	0.5	3.3	145	142	4.0	3.7
6	54	M	162/98	142/96	16.0	14.8	0.4	3.2	143	136	4.1	3.4
7	46	F	190/114	196/106	12.0	12.3	1.1	1.9	144	142	4.5	4.2
8	63	M	175/86	157/78	17.9	14.7	0.8	3.1	140	141	4.0	4.2
9	30	M	140/81	133/74	21.4	15.5	0.4	4.2	140	136	4.2	3.4
10	52	M	204/110	144/91	22.3	20.4	1.0	5.4	143	141	4.5	4.6
11	51	F	204/112	166/92	18.2	16.3	0.8	1.6	143	140	4.2	3.7
12	50	M	144/112	132/88	18.0	15.7	0.9	6.5	145	143	3.8	3.2
Group means			175/106	151/94	18.2	16.1	0.7	3.2	141	139	4.0	3.6
SED			2.8		0.4		1.1		0.5		0.02	
p			<.001		<.001		<.001		<.001		<.001	
B. Spironolactone treatment												
1	44	M	149/110	160/112	22.7	21.6	0.4	5.5	148	138	3.5	4.0
2	35	F	184/126	154/106	15.4	14.7	1.3	2.7	141	142	4.3	4.6
13	50	F	161/101	126/86	17.3	15.8	0.4	1.1	138	135	4.2	4.5
14	47	M	158/103	146/90	20.0	18.1	1.6	2.9	142	139	4.4	4.9
15	42	M	176/117	153/109	19.0	17.0	0.9	7.4	138	131	4.0	4.5
16	57	F	155/95	127/83	14.4	12.6	1.6	3.3	141	138	3.8	4.7
17	50	F	170/100	125/80	21.0	16.0	0.4	5.6	140	136	3.8	4.6
18	42	M	186/128	168/118	20.3	18.6	0.5	2.7	141	138	3.5	4.8
19	54	M	164/100	148/104	21.5	18.0	1.8	6.4	142	135	3.6	4.4
20	51	M	184/124	184/110	16.7	16.0	0.5	2.3	144	137	4.3	4.8
21	58	F	156/96	124/73	13.8	12.6	0.6	3.6	147	139	4.1	4.2
22	63	M	148/112	154/112	17.6	17.1	0.8	4.6	144	140	3.9	4.4
23	62	M	148/109	124/90	16.2	14.3	1.0	1.7	146	139	3.9	4.7
24	63	F	174/98	119/83	13.6	10.6	0.2	3.4	138		3.3	5.7
Group means			165/109	144/97	18.0	16.2	0.8	3.7	142	137	3.9	4.6
SED			1.6		0.28		0.37		0.6		0.06	
p			<.001		<.001		<.001		<.001		<.001	

C = control observation; D = observations during drug treatment; SED = standard error of the difference; for arterial pressure this represents SED for diastolic only.

Table 2.—Statistical evaluation of the relationships of percentile changes in plasma renin activity to percentile changes in plasma volume, serum sodium concentration, and diastolic arterial pressure

		Plasma volume		Serum sodium		Diastolic blood pressure	
Treatment groups	No.	r*	p	r	p	r	p
Hydrochloro-thiazide	12	+.472	n.s.	+.322	n.s.	+.167	n.s.
Spironolactone	14	+.533	<.05	−.414	n.s.	+.045	n.s.
Both	26	+.461	<.02	−.277	n.s.		

* r = correlation coefficient.
n. s. not significant.

for both groups were combined there was a significant relationship between the percentile decreases and elevations of plasma renin activity ($r = +.461$, $p < .02$) (*Fig. 1*). However, when data from each group were handled separately, a significant association was found in the spironolactone-treated group ($r = +.533$, $p < .05$), but not among patients receiving hydrochlorothiazide ($r = +.474$, $p < 0.1$). In the latter group, although the correlation coefficient suggested a relationship, the group was too small ($n = 12$) to represent a statistically significant association.

Both diuretics reduced serum sodium concentration. Although this reduction was greater in the spironolactone-treated patients, it was not significantly different from the reduction produced by hydrochlorothiazide. There was no correlation between percentile reduction in serum sodium concentration and percentile increases in PRA (*Table 2*) in either group. However, in the spironolactone-treated patients, the measured serum sodium concentration correlated inversely and significantly with the actual value for plasma renin activity ($r = -.517$, $p < .05$). No association was found between serum potassium concentration and PRA with either treatment.

Discussion

Short-term experiments in man and in dogs have provided ample evidence that plasma renin activity is influenced by intravascular volume,[20, 21] arterial pressure,[8, 9, 22] neural activity,[23, 24] and

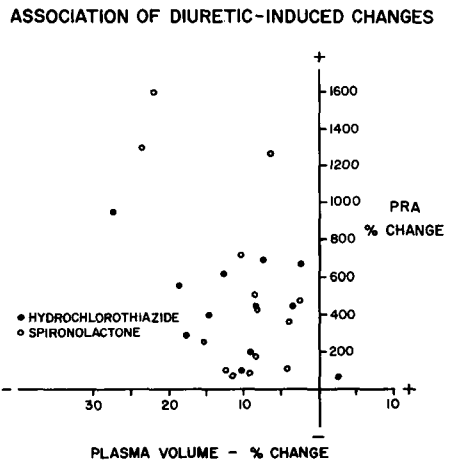

Fig. 1. Relationship between rise in PRA and fall in plasma volume in hypertensive patients during long-term treatment with hydrochlorothiazide (closed circles) and spironolactone (open circles), correlation coefficient (r) .461, $p < .02$.

plasma concentrations of sodium[10] and potassium.[11, 12, 25, 26] Less well explored is the possibility that these factors operate quantitatively during chronic illnesses and their treatments.

In this study, the significant correlation between percentile reductions of PV and elevations of PRA suggests that chronic oligemia plays an ongoing role in renin production and release during months and years of diuretic treatment. That this is in some way an effect of oligemia, rather than of the diuretics themselves, is supported by our previous finding[7] of an inverse relationship between intravascular volume and PRA in normal men, men with essential hypertension, and patients with renovascular hypertension. A similar suggestion concerning blood volume-renin relationships had come from a study of the effects of discontinuing long-term hydrochlorothiazide treatment.[1] We found that during the first week without the diuretic PV rose and elevated levels of PRA decreased to normal. Although this suggested a suppression of renin release by intravascular volume expansion, decrease of PRA could have reflected merely lack of a direct diuretic-stimulating effect. However, more recently, we have shown[27] that during treatment with hydrochlorothiazide or spironolactone or both, PRA can be substantially reduced by rapid intravascular volume expansion with dextran in either 5% glucose or isotonic sodium chloride solutions even though dextran in glucose decreased serum sodium concentration substantially. These results suggest that regardless of any direct renal effects of diuretics on renin production and release,[13, 28] intravascular volume plays a role in determining the level of plasma renin activity. How this operates is not known but possible explanations are modification of stretch receptors in afferent arterioles,[29] of sympathetic vasomotor outflow to the kidneys,[23] and of proximal tubular sodium reabsorption that would determine the amount of sodium reaching the macula densa.[30]

In regard to intravascular volume-PRA relationships, it should be mentioned that before treatment an inverse correlation was not found in these patients as previously reported for essential hypertension.[7] Since this was a retrospective study of the effects of two diuretics on PRA, the group contained a number of patients with "hypervolemic essential hypertension" who, because of either expanded plasma volume or plasma volume inappropriately normal for the height of diastolic arterial pressure, were expected to respond well to diuretic treatment.[19] Further, PRA was lower and the range of values more limited than usually found in hypertensive patients.[7] Thus, neither plasma volume nor plasma renin activity was representative for the spectrum of essential hypertension.

Long-term interrelationships of arterial pressure and the renal pressor system remain obscure. In this study we failed to find an association between arterial pressure reduction and increases of PRA. This may indicate that in hypertensive patients so treated, whatever pressure is achieved reflects the sum of the depressor potential of the drug and the pressor potential offered by substantial increases of PRA. In fact, these increases are of a magnitude often found in patients with renovascular hypertension, a condition in which we have found evidence for a direct relationship be-

tween severity of hypertension and peripheral PRA. As yet there is no understanding of the mechanism whereby diuretic drugs lower arterial pressure, and at the same time raise PRA.

There is considerable evidence that plasma sodium concentration plays a role in renin production or release or both, not only in animal studies of brief duration,[31] but also in chronic illness.[10] In renal perfusion studies in dogs, Nash et al[31] evoked renin release by lowering sodium concentration and then suppressed it by increasing sodium concentration. In regard to these relationships in chronic illness, Brown et al[10] found an inverse association between serum sodium and renin concentrations in a large group of patients with a broad spectrum of hypertensive disorders. The same relationship was found between serum sodium concentration and PRA obtained in our spironolactone-treated patients, but not in those receiving hydrochlorothiazide. Both diuretics decreased serum sodium concentration and, although the spironolactone decrease was greater, it was not significantly so. These effects on sodium concentration are similar to those obtained by Morrison and Sebestyn[32] in a comparative study of the two diuretics. They found, during two weeks of treatment, that although hydrochlorothiazide increased urine volume more than spironolactone, each produced the same degree of negative sodium balance, and that as a consequence spironolactone treatment was associated with greater decreases in serum sodium concentration.

Our failure to find a relationship between serum sodium and PRA with hydrochlorothiazide administration is not readily explainable. Considering the kaliopenic effect of this diuretic and the recent demonstrations of an inverse relationship between serum potassium concentration and renin,[11, 12, 25, 26] one might expect to find that PRA enhancement by hyponatremia would be reinforced by decreases in serum potassium. Conversely, the finding of an inverse relationship between serum sodium concentration and PRA during spironolactone treatment was unexpected since serum potassium was maintained at levels that could conceivably blunt the effects of hyponatremia.

Whatever the influence of these plasma electrolyte concentrations on renin release may be, it seems capable of being over-ridden by extracellular fluid expansion. As referred to above,[27] elevated PRA found during hydrochlorothiazide or spironolactone treatment or both could be quickly suppressed by rapid intravascular volume expansion whether or not serum sodium value fell. Also, Newsome and Bartter[33] showed in experiments of several days' duration that overhydrating normal persons suppressed both PRA and serum sodium. Further, plasma renin concentration has been found to be normal or low in patients with inappropriate ADH secretion and marked hyponatremia[34, 35] and high in association with dehydration and hypernatremia.[35]

This study provides no information concerning different direct effects of these two drugs on the juxtaglomerular apparatus. If there are differences, it seems likely that the similar extrarenal effects on plasma volume and sodium concentration were enough to obscure them. Vander[13, 30] has proposed that renin release is reg-

ulated by the amount of sodium reaching the macula densa area and by the ability of these cells to reabsorb it. He suggests that furosemide and probably other chlorothiazide diuretics impair this transport function. Since both oligemia and hyponatremia diminish the filtered sodium load and thereby influence fractional sodium reabsorption by the proximal tubule,[36] this would limit the amount of sodium reaching more distal portions of the nephron, the macula densa, and the area where Na^+-K^+ exchange is influenced by aldosterone. Thus, as in this study, the oligemic and hyponatremic effects of two dissimilar diuretics could so restrict the distal sodium load as to obscure any difference between a macula densa blockade by hydrochlorothiazide and a more distal aldosterone antagonism by spironolactone.

Considering the number of factors now known to stimulate renin release, the number that will probably be found related to renin production, as well as the complexities of the renin-renin substrate reaction, it is unlikely that a clinical study such as this can describe a one-for-one relationship between a factor releasing renin and PRA. It may be possible, however, that a multifactorial analysis can describe the relative importance of each of the various factors.

Summary

Mechanisms whereby plasma renin activity becomes elevated during chronic treatment with two dissimilar diuretics, hydrochlorothiazide and spironolactone, were studied in patients with uncomplicated, essential hypertension. Twelve patients were given hydrochlorothiazide (50 mg/day) and 14 received spironolactone (100 mg/day) for 3 to 11 months. Each patient measured his arterial pressure twice daily. Plasma renin activity (PRA), plasma volume (PV), and serum sodium and potassium concentrations were measured before and several times during treatment. Except that serum potassium was significantly reduced by hydrochlorothiazide ($p < .001$) and elevated by spironolactone ($p < .001$), effects of the two diuretics were similar. PRA increased equally; sodium, PV, and blood pressure decreased equally; all changes were significant at $p < .001$. For the two groups combined, increase in PRA correlated directly with plasma volume reduction ($r = +.461$, $p < .02$), but not with decrease of arterial pressure or percentile changes in serum sodium and potassium. However, in spironolactone-treated patients serum sodium concentration and PRA were inversely associated ($r = -.517$, $p < .05$). The data suggest that chronic oligemia is an important determinant of PRA in diuretic-treated patients, and that plasma sodium concentration may also be a factor.

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