Changes in Plasma Renin Activity after Administration of Spironolactone

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Spironolactone, a potent aldosterone-blocking agent, was administered to 34 subjects including 4 patients with primary aldosteronism, and changes in plasma renin activity and electrolytes were followed up. Plasma renin activity was found to elevate during the medication in all subjects except 4, who were suffering from primary aldosteronism. In the latter subjects there was no increase in the renin activity. A possibility was suggested with regard to the differential diagnosis of primary aldosteronism from other mimicking hypertension using this spironolactone test.

IT HAS BEEN well known that the renin-angiotensin system is activated in response to renal hemodynamic changes and that this system stimulates the secretion of aldosterone, which reciprocally suppresses the release of renin from the kidneys. Recently CONN et al.¹⁾ proposed that primary aldosteronism can be differentiated from other types of hypertension when changes in plasma renin activity is followed before and after the patient is subjected to sodium depletion and taking upright posture, because the renin activity is regularly increased by these treatments in all patients with hypertension except ones with primary aldosteronism.

During our studies on plasma renin activity, spironolactone, a potent aldosterone-blocking agent, was observed to elevate plasma renin activity in many subjects except in patients with primary aldosteronism. These findings suggested that spironolactone could be utilized for the purpose of screening test of primary aldosteronism.

MATERIALS AND METHODS

Thirty-four subjects were chosen for this

experiment. As controls, 11 normal subjects aged 15 and 48 years, 6 men and 5 women, were selected. Remaining 23 patients consisted of 6 benign essential hypertension, 6 renovascular hypertension, 1 coexistence of renovascular hypertension and pheochromocytoma, 2 pheochromocytoma, 1 Cushing syndrome, 1 coarctation of the aorta, 1 polycystic kidney, 1 chronic glomerulonephritis and 4 primary aldosteronism. Diagnosis was made by physical and laboratory examinations, in all of them except 6 patients with benign essential hypertension and 1 with chronic glomerulonephritis it was verified by operation. During the course of this study, the subjects were allowed to be ambulatory, and they were on a hospital diet. Blood sampling from the subjects was made in bed after overnight fast.

The method for determination of plasma renin activity has been reported previously from this laboratory²⁾³⁾.

RESULTS

Preliminary Study

As a preliminary study, spironolactone (Aldactone-A, Searle, 400 mg per day) was

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Fig. 1. Responses in blood pressure, plasma electrolytes and plasma renin activity to the administration of Aldactone-A 400 mg/day in a normal volunteer.

given to 3 normal volunteers for 10 days. Plasma renin activity and plasma electrolytes (sodium and potassium) were determined before, on the 3rd, 5th, 7th and 10th days of the medication, and on the 5th day after its cessation. Fig. 1 shows a typical response in blood pressure, plasma electrolytes and plasma renin activity to the administration of Aldactone-A. No side effect was observed up to the 5th day of the drug administration, but anorexia, nausea and rash with itching usually appeared after the 6th day. When the drug was discontinued, the side effects subsided within a day or so. In all of the 3 subjects, the renin activity increased progressively with the administration of the drug. Of samples, on the 7th and 10th days plasma renin activity was found to be no more significantly increased than that on the 5th day. The drug also gave changes in plasma electrolytes; decrease in sodium and increase in potassium. But after the withdrawal of Aldactone-A, all values of plasma electrolytes and plasma renin activity returned to control levels.

From these observations, 5 days administration was finally selected because of significant

increase in plasma renin activity and no side effects. The dose of Aldactone-A was chosen to be 400 mg per day according to the study of BIGLIERI et al.⁴⁾

Normal Subjects

In normal subjects, plasma renin activity was below 2.0 μg equivalent to synthetic angiotensin per liter of plasma. In the present study, therefore, the renin activity was considered to be increased when it was 2.0 μg per liter of plasma or greater.

The data are summarized in Table I. In 4 cases the renin activity was assayed on the 3rd day of the administration of the drug and was found to increase. On the 5th day the activity was markedly elevated in all cases, ranging 3.8–8.6 μg per liter of plasma. Plasma sodium concentration decreased by 5 mEq per liter or more on the same day. However, on the 5th day after cessation of the drug, the renin activity and electrolytes restored to their control values. When excessive amounts of salt were medicated simultaneously with spironolactone, the renin activity remained in all subjects tested.

Hypertensive Subjects

TABLE I RESPONSES OF PLASMA RENIN ACTIVITY AND PLASMA ELECTROLYTES IN NORMOTENSIVE SUBJECTS BY ADMINISTERING ALDACTONE-A 400 MG PER DAY

Subjects	Before administration		3rd day		5th day		7th day		10th day		5th day after withdrawal	
	Plasma Na & K (mEq/L)	Renin activity (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)
Y.K. 47 m	142.5 4.0	0.8	142.0 4.3	2.0	137.0 4.2	3.8	135.5 4.5	4.5	135.5 4.7	5.0	140.0 4.0	0.8
T.K. 15 m	142.5 4.1	1.9			135.5 4.3	4.0	137.5 4.3	7.8	137.5 4.4	9.0	142.0 4.1	2.0
K.S. 36 m	140.0 4.3	1.4		2.1	135.0 4.7	4.3		7.1			140.0 3.8	0.9
R.S. 37 m	139.1 3.8	0.7			136.7 4.3	6.7					140.5 3.9	0.8
N.T. 48 m	139.1 3.8	0.8			136.1 4.3	6.1					143.2 3.9	0.3
T.T. 48 m	142.5 4.1	1.0			133.5 4.7	3.8					140.5 4.2	0.9
Y.C. 42 f	145.1 4.0	0.7	141.4 4.0	3.0	136.1 3.9	5.5					143.2 4.1	0.8
M.C. 21 f	139.0 4.5	1.2			137.1 4.7	7.7					140.0 4.3	1.3
Y.K. 21 f	140.5 4.2	0.9			137.5 4.5	4.8					140.0 3.8	1.3
F.K. 38 f	140.0 3.7	0.7			137.0 3.9	5.9					139.6 3.6	0.8
T. I. 41 f	139.6 3.4	1.0			137.1 3.6	8.6					140.0 3.5	0.8

In patients with benign essential hypertension, coarctation of the aorta and chronic glomerulonephritis, each of their first samples gave normal value in plasma renin activity, whereas all of the patients with renovascular hypertension, 2 patients with pheochromocytoma, 1 with coexistence of pheochromocytoma and renal artery stenosis and 1 with polycystic kidney gave the values above normal before Aldactone-A administration. Medication of the drug enhanced the renin activity in these patients as in normal subjects as shown in Table II.

On the contrary, in 4 patients with primary aldosteronism the renin activity remained unchanged, fluctuating within normal range. To confirm this finding, the same experiments were repeated several weeks later in 3 cases (A.N., M.F. and K.N.). Their renin activities failed again to increase. After removal of adenomas from the adrenal glands, however, the renin activities responded to Aldactone-A with the same fashion as in normal subjects.

DISCUSSION

Spironolactone alters plasma electrolytes

concentrations, decrease in sodium and increase in potassium, by its action on the renal tubules. These changes in plasma have been already recognized as a factor which induces aldosterone secretion by the adrenal glands⁵⁻⁷. When spironolactone is administered to man, an increase in aldosterone secretion could be expected and this has been confirmed by several investigators^{8,9}.

Now the specific stimulator of aldosterone output is known to be angiotensin, a pressor polypeptide produced by renin. Therefore, spironolactone administration must result in an increased release of renin from the kidneys. This proved in the present study in all subjects tested, except in patients with primary aldosteronism. An increase of renin evoked by spironolactone seemed to be due to the sodium depleting effect of the drug or to hypovolemia resulting decreased plasma sodium concentration.

As presented above, however, in patients with primary aldosteronism plasma renin activity did not increase during spironolactone administration. These findings could be applicable to differentiate primary aldosteronism

TABLE II RESPONSES OF PLASMA RENIN ACTIVITY AND PLASMA ELECTROLYTES IN HYPERTENSIVE PATIENTS BY ADMINISTERING ALDACTONE-A 400 MG PER DAY

Subjects	Diagnosis	Blood pressure (mmHg)	Before administration		5th day		5th day after withdrawal	
			Plasma Na & K (mEq/L)	Renin activity (μ g/L)	Na & N (mEq/L)	Renin (μ g/L)	Na & K (mEq/L)	Renin (μ g/L)
T.E. 3 m	Essential hypertension	162/112	142.5 3.5	1.8	136.0 3.8	9.6	140.5 3.6	1.6
T.S. 35 m	Essential hypertension	170/100	137.5 3.7	0.8	133.5 3.8	2.1	140.0 3.7	1.3
K.W. 47 m	Essential hypertension	160/ 90	142.5 4.2	0.3	137.0 4.6	2.5	142.5 4.1	0.9
K.Y. 60 m	Essential hypertension	160/100	142.5 4.5	1.5	136.1 4.5	3.9	136.5 4.0	1.7
A.S. 32 f	Essential hypertension	176/120	140.5 4.2	1.7	135.0 4.4	4.6	138.5 4.0	1.5
N.S. 50 f	Essential hypertension	180/ 96	138.0 3.9	0.8	133.0 4.2	2.8	137.5 4.0	0.9
A.S. 15 m	Renovascular hypertension	156/ 60	140.0 4.5	5.4	137.0 4.5	12.6	142.3 4.5	4.8
T.O. 15 m	Renovascular hypertension	160/ 90	140.0 4.2	2.2	137.0 4.6	6.0	140.5 4.4	2.4
E.M. 17 f	Renovascular hypertension	174/102	137.6 3.3	2.7	135.0 3.5	7.3	137.5 3.2	3.1
K.M. 17 f	Renovascular hypertension	194/ 82	142.5 3.6	2.8	135.0 4.6	7.1	138.6 3.5	2.2
M.K. 18 f	Renovascular hypertension	182/118	140.5 3.8	2.8	135.0 4.3	5.7	140.0 4.1	3.2
K.Y. 33 f	Renovascular hypertension	156/110	140.5 4.0	3.3	135.0 4.2	4.2	140.5 4.0	2.7
S.O. 21 f	Coexistence of renovascular hypertension & pheochromocytoma	160/ 80	140.5 4.0	3.0	135.0 4.3	6.7	140.5 4.1	2.6
T.T. 25 m	Pheochromocytoma	190/108	140.5 4.3	2.7	135.0 4.6	4.5	141.0 4.3	2.5
M.F. 45 f	Pheochromocytoma	228/148	137.5 3.8	4.8	133.5 4.0	18.7	136.5 3.9	7.1
R.N. 22 f	Coarctation of the aorta	210/100	133.5 3.8	0.8	130.5 4.1	4.8	136.0 3.9	0.9
T.K. 36 m	Cushing syndrome	220/140	145.0 3.8	2.0	140.5 3.6	9.1	145.0 3.6	1.2
T.T. 34 m	Polycystic kidney	180/110	140.5 4.0	3.0	133.5 4.4	5.2	139.6 3.9	2.8
M.T. 31 f	Chronic glomerulonephritis	160/ 90	137.0 5.1	0.5	137.5 6.3	2.6	138.0 6.2	0.5
C.O. 43 m	Primary aldosteronism	180/100	142.6 1.7	1.1	140.8 2.3	0.5		1.8
A.N. 35 m	Primary aldosteronism	152/110	147.5 2.2	1.0	140.5 3.5	1.5	142.5 2.5	1.1
	preoperative period		142.5 2.5	1.1	137.5 2.5	1.1	145.0 2.3	1.0
	postoperative period		145.0 4.4	0.8	140.5 4.3	4.9	142.0 4.3	0.8
M.F. 41 f	Primary aldosteronism	206/120	143.0 2.3	0.6	140.8 2.3	0.7	140.0 2.2	0.5
	preoperative period		142.5 2.6	0.9	140.0 2.6	0.6	141.8 2.4	0.8
	postoperative period		140.8 3.7	0.7	138.2 4.0	2.6		0.5
K.N. 46 f	Primary aldosteronism	184/ 92	139.6 2.9	1.3	135.0 3.6	0.6	140.5 3.2	0.8
	preoperative period		140.5 3.0	0.9	135.6 3.8	0.7	139.0 3.2	1.2
	postoperative period		137.0 3.5	1.8	135.5 4.0	4.9		1.7

from other hypertensive diseases. However, the reason of this lack of response is not clear. The following possibilities may be supposed. Since the adenoma produces large amounts of aldosterone, perhaps the dose of spironolactone used in this study is not enough to inhibit the action of the hormone. Moreover, an increase of plasma potassium induced by spironolactone enhances aldosterone secretion from the tumor.

If subjects under examination take excessive amounts of salt in their diet, the test may lead to falsely positive. However, under the usual amount of salt intake, equivocal result has never encountered as presented in the chapter of experiment. Consequently, this study may be more applicable to differentiate primary aldosteronism from other mimicking diseases, when compared with the Conn's method¹⁾, which consisted of combination of restriction of daily salt intake less than 10 mEq and taking upright posture, since the present procedure might be performed without severe deprivation of salt. Along this line, studies are now under progress in our laboratory.

SUMMARY

To study the effect of spironolactone on plasma renin activity, 400 mg of Aldactone-A were administered daily to 11 normal subjects and 23 hypertensive patients including 4 patients with primary aldosteronism for 5 days. Plasma renin activity was found to increase significantly during the medication of the drug in all subjects except 4 patients with primary aldosteronism. In primary aldosteronism, there was no increase in the renin activity. To confirm this finding, the same experiments

were repeated in 3 cases several weeks later. The renin activity failed again to increase. However, after removal of adrenocortical adenoma, plasma renin activity responded to the drug with the same fashion as in normal subjects.

When this finding is applied in differential diagnosis of primary aldosteronism, it would become more applicable screening test in comparison with the Conn's method, since the present procedure is able to perform without severe restriction of salt intake.

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ADDENDUM

While this paper was in press, suppression of plasma renin activity during the treatment of spironolactone was confirmed in an additional case of primary aldosteronism.