A SIMPLIFIED SCREENING TEST FOR DIFFERENTIATING PRIMARY ALDOSTERONISM FROM ESSENTIAL HYPERTENSION WITH LOW PLASMA RENIN ACTIVITY

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A simplified screening test for differentiating primary aldosteronism (PA) from low renin essential hypertension (LREH) is presented.

Nine patients with LREH and 5 patients with PA due to adrenal adenoma were studied. In the patients with LREH, the levels of plasma renin activity (PRA) before and after treatment with furosemide (0.7 mg/kg, i.v.) and a 2-hour ambulation under treatment with dexamethasone (1.0 mg) (dexamethasone + furosemide test) increased briskly, compared to the levels of PRA before and after treatment with furosemide (0.7 mg/kg, i.v.) and a 2-hour ambulation (furosemide test). In patients with PA, there was no significant difference between the mean levels before the furosemide test and before the dexamethasone + furosemide test, or between the mean levels after the furosemide test and after the dexamethasone + furosemide test.

These results suggest that the suppression of PRA in patients with LREH may be related to a factor controlled by dexamethasone. It is concluded that the dexamethasone + furosemide test is useful for differentiating PA due to adenoma from LREH.

DESPITE extensive investigations, the exact genesis of essential hypertension (EH) with low plasma renin activity has not yet been clarified. Some previous papers have described several factors for the suppression of plasma

renin activity (PRA) in patients with low renin essential hypertension (LREH).¹⁻⁹ Whatever mechanisms are actually involved in the suppression of PRA, it is important to make a differential diagnosis between LREH and primary aldosteronism (PA), since some patients with LREH show as low levels of PRA as those found in patients with PA.

Recently, we reported that a stimulation test with administration of furosemide under dexamethasone treatment in patients with LREH significantly raised the PRA to the normal range, and that one of the factors involved in the sup-

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Abbreviation used in this paper is: aldosterone: 11 β , 21-dihydroxy-18-oxo-4-pregnene-3, 20-dione.

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TABLE I CLINICAL AND LABORATORY FINDINGS IN PATIENTS WITH LOW RENIN ESSENTIAL HYPERTENSION (LREH) AND PRIMARY ALDOSTERONISM (PA)

Patient	Age (years)	Sex	Blood pressure (mmHg)		Serum electrolytes (mEq/L)	
			Syst.	Diast.	Na ⁺	K ⁺
I) LREH group						
1	45	M	156	88	146	4.0
2	44	M	158	90	143	4.0
3	26	M	170	100	145	4.1
4	42	M	140	98	143	3.7
5	41	M	140	110	144	3.9
6	39	M	166	120	147	3.8
7	36	M	160	120	143	3.4
8	38	M	164	116	144	3.7
9	28	M	160	90	143	4.1
Mean	38		157	104	144	3.9
± S.D.	6		10	13	2	0.3
II) PA group						
1	47	F	170	120	146	3.1
2	34	F	186	120	141	3.1
3	39	F	148	90	143	1.7
4	31	M	180	120	148	2.7
5	34	M	160	100	145	2.0
Mean	37		169	110	145	2.5*
± S.D.	6		14	13	2	0.6

Significance vs. patients with LREH: * = $P < 0.01$.

pression of PRA in LREH might be ACTH dependent.⁷

In the present study, we investigated the responses of PRA to administration of furosemide under dexamethasone treatment in patients with LREH and patients with PA. This stimulation test was found to be useful for the differential diagnosis of these two diseases.

MATERIALS AND METHODS

Subjects:

Nine patients with LREH and 5 patients with PA were studied. The diagnosis of LREH was made after excluding known causes of hypertension, by renal arteriography, urinary catecholamine determination, and measurements of steroids in the renal venous plasma, peripheral plasma and urine. Patients showing a PRA of less than 1.0 ng/ml/hr after the intravenous administration of furosemide (0.7 mg/kg, i.v.) and a 2-hour ambulation (furosemide test) were considered to be LREH. Furthermore, it was

certified that the levels of plasma aldosterone in patients with LREH were suppressed by saline infusion (1000 ml/hr, 1 hour).

The diagnosis of PA due to adenoma was made by renal and adrenal arteriography, adrenal scintigrams and measurements of peripheral plasma and adrenal venous plasma steroids. Two patients with LREH (Table I, No. 8 and No. 9) and 5 patients with PA underwent a laparotomy. The 5 patients with PA were all found at laparotomy to have an adrenal adenoma, which was removed with cure of the hypertension and hypokalemia. They displayed very low plasma aldosterone levels in the postoperative period. On the other hand, 2 patients with LREH could not be found to have an adrenal adenoma.

Antihypertensive therapy had been withheld for at least 2 weeks prior to the present study, and all experiments were performed on a diet containing 5–8 grams NaCl/day.

TABLE II CIRCADIEN LEVELS OF PLASMA ALDOSTERONE (ng/dl) IN PATIENTS WITH LOW RENIN ESSENTIAL HYPERTENSION (LREH) AND PRIMARY ALDOSTERONISM (PA)

Patient No.	Time			
	0600 h	1600 h	2400 h	Total#
I) LREH group				
1	8.6	7.8	11.4	27.8
2	8.6	5.9	6.3	20.8
3	11.4	10.0	6.5	27.9
4	5.5	1.6	3.9	11.0
5	9.4	6.3	8.1	23.8
6	3.1	4.7	0.4	8.2
7	2.2	1.6	1.3	5.1
8	26.5	11.8	10.8	49.1
9	19.6	12.9	10.2	42.7
Mean	10.5	7.0	6.5	24.0
± S.D.	7.4	3.9	3.8	14.1
II) PA group				
1	25.8	14.3	25.9	66.0
2	23.6	10.9	6.1	40.6
3	26.8	28.8	16.3	71.9
4	52.8	24.7	17.6	95.1
5	23.0	10.0	10.0	43.0
Mean	30.4**	17.7**	15.2*	63.3**
± S.D.	11.3	7.6	6.8	20.1

Significance vs. patients with LREH: ** = $p < 0.01$, * = $p < 0.02$.

: Total of each value in the circadian rhythm.

Test procedures:

1. Circadian rhythm of plasma aldosterone:

Blood samples for assessing the circadian rhythm of plasma aldosterone were drawn at 0600, 1600 and 2400 h in recumbent position. However, blood samples at 1600 h were drawn after 2-hour recumbency from 1400 h.

2. Furosemide test:

Immediately after the base line sample had been drawn at 0900 h after overnight recumbency, furosemide (0.7 mg/kg) was administered intravenously. After 2 hours ambulation, another blood sample was collected for determination of steroid hormones and PRA.

3. Dexamethasone + furosemide test:

One mg of dexamethasone was administered orally at 2100 h, and on the next morning the base line sample was drawn at 0900 h after overnight recumbency. Immediately after this, furosemide (0.7 mg/kg) was administered intravenously. After 2 hours ambulation, another

blood sample was collected for determination of steroid hormones and PRA.

These tests were done at intervals of 5–6 days. Plasma aldosterone was measured as previously reported¹⁰ PRA was measured by using a kid of CEI-IRE-SORIN. Statistical comparisons were made by Student's t test.

RESULTS

Table I lists the age, sex, blood pressure and serum electrolyte concentrations of 9 patients with LREH and 5 patients with PA. There was no significant difference in age, blood pressure or serum sodium levels between the LREH and PA groups. However, the patients with PA revealed significantly lower plasma potassium levels than those with LREH ($P < 0.01$).

The circadian levels of plasma aldosterone in the 2 groups of patients are shown in Table II. The levels of plasma aldosterone at 0600, 1600 and 2400 h in patients with PA were significantly

TABLE III LEVELS OF PLASMA RENIN ACTIVITY (PRA) AND PLASMA ALDOSTERONE BEFORE AND AFTER TREATMENT WITH FUROSEMIDE (0.7 mg/kg, i.v.) AND A 2-HOUR AMBULATION TEST IN PATIENTS WITH LOW RENIN ESSENTIAL HYPERTENSION (LREH) AND PRIMARY ALDOSTERONISM (PA)

Patient No.	P R A (ng/ml/hr)		Aldosterone (ng/dl)	
	Before	After	Before	After
I) LREH group				
1	0.6	0.9	13.3	13.7
2	0.6	0.7	17.3	47.9
3	0.5	0.9	5.9	10.0
4	0.2	0.5	3.5	10.2
5	0.3	0.6	9.8	14.5
6	0.2	0.5	7.5	12.2
7	0.6	0.9	8.1	10.0
8	0.3	0.5	20.5	39.3
9	0.7	0.6	13.2	48.4
Mean	0.4	0.7***	11.0	22.9*
± S.D.	0.2	0.2	5.2	16.0
II) PA group				
1	0.5	0.9	24.3	55.0
2	0.1	0.1	31.0	36.0
3	0.2	0.2	17.8	50.7
4	0.2	0.4	29.5	50.5
5	0.2	0.3	20.0	35.7
Mean	0.2	0.4	24.5##	45.6***
± S.D.	0.1	0.3	5.1	8.1

Significance vs. base line levels of PRA or plasma aldosterone: *** $p < 0.01$, ** $p < 0.02$, * $p < 0.05$.
Significance vs. patients with LREH: ## = $p < 0.01$, # = $p < 0.02$.

higher than those in patients with LREH ($P < 0.01$, $P < 0.01$ and $P < 0.02$, respectively). Furthermore, the mean total values of plasma aldosterone in the circadian rhythm were 24.0 ± 14.1 (S.D.) ng/dl in patients with LREH and 63.3 ± 20.1 ng/dl in patients with PA. This difference was significant ($P < 0.01$). In 2 out of 9 patients with LREH (Nos. 8 and 9), the total values of plasma aldosterone were as high as the levels found in the patients with PA.

The levels of PRA before and after the furosemide test were 0.4 ± 0.2 (S.D.) and 0.7 ± 0.2 ng/ml/hr in patients with LREH, and 0.2 ± 0.1 and 0.4 ± 0.8 ng/ml/hr in patients with PA, respectively (Table III). There was no significant difference between the groups in the levels of PRA before or after the furosemide test. However, the levels of PRA after the furosemide test in the patients with LREH were significantly increased from the base line levels ($P < 0.01$).

The levels of plasma aldosterone before and after the furosemide test were 11.0 ± 5.2 (S.D.) and 22.9 ± 16.0 ng/dl in patients with LREH and 24.5 ± 5.1 and 45.6 ± 8.1 ng/dl in patients with PA, respectively. The levels of plasma aldosterone after the test were significantly increased from the base line levels in each group ($P < 0.05$ and $P < 0.02$, respectively). When compared with the LREH group, the PA group showed significantly higher levels of plasma aldosterone before and after the furosemide test ($P < 0.01$ and $P < 0.02$, respectively).

The levels of PRA and plasma aldosterone before and after the dexamethasone + furosemide test are listed in Table IV. The levels of PRA after the test were significantly increased from the base line levels in both the LREH and PA groups ($P < 0.01$ and $P < 0.05$, respectively). The levels of PRA before and after the test in patients with PA were significantly lower than

TABLE IV LEVELS OF PLASMA RENIN ACTIVITY (PRA) AND PLASMA ALDOSTERONE BEFORE AND AFTER TREATMENT WITH FUROSEMIDE (0.7 mg/kg, i.v.) AND A 2-HOUR AMBULATION TEST UNDER DEXAMETHASONE (1.0 mg) IN PATIENTS WITH LOW RENIN ESSENTIAL HYPERTENSION (LREH) AND PRIMARY ALDOSTERONISM (PA)

Patient No.	P R A (ng/ml/hr)		Aldosterone (ng/dl)	
	Before	After	Before	After
I) LREH group				
1	2.0	7.0	6.6	7.0
2	0.8	3.0	4.7	8.5
3	0.6	2.0	6.8	8.0
4	2.1	3.5	1.7	4.3
5	1.2	4.4	8.2	16.1
6	0.2	1.0	4.3	9.3
7	2.8	6.1	4.5	5.5
8	0.7	2.3	2.4	1.6
9	1.0	3.0	8.2	24.2
Mean	1.3 ^{☆☆}	3.6 ^{***☆☆}	5.3 [*]	9.4 ^{☆☆}
± S.D.	0.8	1.8	2.2	6.5
II) PA group				
1	0.8	0.9	13.3	20.4
2	0.1	0.3	5.3	6.5
3	0.3	0.3	26.6	50.6
4	0.2	0.4	14.6	22.7
5	0.2	0.3	10.2	25.0
Mean	0.3 [#]	0.4 ^{###}	14.0 ^{##}	25.0 ^{*##}
± S.D.	0.2	0.2	7.1	14.3

Significance vs. base line levels of PRA or plasma aldosterone: ** = $p < 0.01$, * = $p < 0.05$.

Significance vs. patients with LREH: ## = $p < 0.01$, # = $p < 0.05$.

Significance vs. levels of PRA or plasma aldosterone before and after treatment with furosemide and a 2-hour ambulation test: ☆☆☆ = $p < 0.01$, ☆☆ = $p < 0.02$, ☆ = $p < 0.05$.

those in patients with LREH ($P < 0.05$ and $P < 0.01$, respectively). Comparison of the levels of PRA before and after the furosemide test in each group revealed significant increases in the levels of PRA before and after the dexamethasone + furosemide test in patients with LREH ($P < 0.01$ and $P < 0.02$, respectively). On the other hand, there was no significant increase in the levels of PRA before and after the dexamethasone + furosemide test in patients with PA. In particular, no overlap in levels of PRA after the dexamethasone + furosemide test was found in the patients with LREH and the patients with PA.

The levels of plasma aldosterone after the dexamethasone + furosemide test were significantly increased from the base line levels in patients with PA ($P < 0.05$ and $P < 0.05$, respec-

tively), although the levels of plasma aldosterone before and after the above test in patients with PA were significantly lower than those before and after the furosemide test ($P < 0.05$ and $P < 0.05$, respectively). However, patients with PA showed significantly higher levels of aldosterone before and after the dexamethasone + furosemide test compared to the levels in patients with LREH ($P < 0.01$ and $P < 0.05$, respectively).

DISCUSSION

In general, it is thought that differential diagnosis of PA and LREH is of great importance, since hypertension due to adenoma is curable. In the present study, 2 out of 9 patients with LREH (No. 8 and No. 9) (Table II) showed as high total values of plasma aldosterone as the levels found

in the patients with PA but they were not found at laparotomy to have an adrenal adenoma. Thus, it is difficult to diagnose PA by only plasma levels of aldosterone.

In our previous studies on EH, we reported a significantly increased response of PRA to the dexamethasone + furosemide test in LREH, compared to normal or high renin patients with EH.⁷ This phenomenon was explained that patients with LREH might secrete an excess of unknown mineralocorticoids to be controlled by ACTH. Interestingly, Sekihara et al.⁸ recently reported that many patients with LREH excrete abnormal quantities of unknown mineralocorticoids, but not all of them excrete the same unknown mineralocorticoids.

So far, there have been many reports concerning suppression of PRA in LREH. Brown et al.² described raised DOC levels in the pathogenesis of hypertension with low PRA, but they were unable to lower the blood pressure by treatment with dexamethasone for 2 weeks. On the other hand, Hoeftagels et al.⁶ reported that dexamethasone restored blood pressure to normal, increased body weight, increased plasma potassium, and increased PRA and aldosterone excretion in 3 young hypertensive women with LREH. More recently, Hamilton et al.¹¹ stated that a fall in blood pressure in response to dexamethasone treatment for 4 weeks was found in EH. They suggested that the fall in blood pressure in response to dexamethasone was associated with suppression of plasma levels of cortisol. However, they did not classify their patients into low, normal and high PRA groups, and they did not find any change in the levels of PRA. As described above, there are several reports concerning the effect of dexamethasone treatment in LREH, but there is no paper about a comparative study in LREH and PA.

Based on our present results, the following are suggested as the possible effects of dexamethasone, in order to explain the increased levels of PRA before and after the dexamethasone + furosemide test in LREH group: 1) increment of renin substrate by dexamethasone,^{12,13} 2) increment of PRA by the diuretic activity of dexamethasone,¹³ 3) direct action of dexamethasone on J.G.Cells, 4) increment of PRA through the suppression of ACTH dependent steroids by dexamethasone, and 5) increment of renin reactivity by dexamethasone.

In our previous studies, we reported that treatment with dexamethasone (1.0 mg) was

unable to affect the concentrations of renin substrate and urinary excretion of sodium in patients with LREH.⁷ Furthermore, in an in vitro study, we found that dexamethasone (0.1 μ g, and 0.2 μ g) did not exert any direct action on renin release.⁷ Therefore, it is suggested that other two factors^{4,5} might increase the levels of PRA after the dexamethasone + furosemide test in LREH. On the other hand, we must consider several mechanisms for the suppression of PRA after the dexamethasone + furosemide test in the PA group.

As shown in Table II, the levels of plasma aldosterone in the circadian rhythm in the PA group were significantly higher than those in the LREH group. Furthermore, as seen from Tables III and IV, the mean percentage decreases in levels of plasma aldosterone before and after the dexamethasone + furosemide test as compared to the levels before and after the furosemide test were 52% and 59%, respectively, in the LREH group, and 43% and 45%, respectively, in the PA group. It is possible, therefore, that these high levels of plasma aldosterone in the PA group affected the mechanism of renin release and suppressed the levels of PRA before and after the dexamethasone + furosemide test. Interestingly, the levels of plasma aldosterone in Cases No.8 and No.9 of the LREH group were suppressed before and after the dexamethasone + furosemide test, while their levels of PRA were increased remarkably after the dexamethasone + furosemide test. Therefore, we can suggest that the levels of PRA and plasma aldosterone in the LREH group might be more ACTH dependent than those in the PA group.

Concerning the renin reactivity in the plasma of patients with low PRA, Brooks et al.⁴ reported decreased kinetics of the renin-renin substrate reaction. Another possibility might, therefore, be considered that dexamethasone can increase the kinetics of renin reactivity in LREH. In the case of patients with PA, it is thought that certain factors, i.e. the higher levels of plasma aldosterone after the dexamethasone + furosemide test in patients with PA compared to those in patients with LREH, hypokalemia, etc., may not increase the kinetics of renin reactivity. However, if the above suggestion is true, it is difficult to explain the mechanism of suppression of PRA in Case No.2 of the PA group, since the levels of plasma aldosterone before and after the dexamethasone + furosemide test were low. Therefore, in this case, another unknown mechanism

for the suppression of PRA might be involved. In addition, the levels of plasma aldosterone in this case as shown in Table II could possibly be controlled mainly by ACTH¹⁴⁻¹⁶

Finally, whatever mechanisms are actually involved in the suppression of PRA in both groups, it is concluded that the dexamethasone + furose-mide test provides a useful and easy tool for the differentiation of PA due to adrenal adenoma from LREH.

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