Clinical Evaluation of the Captopril Screening Test for Primary Aldosteronism

Shojiro NAOMI, M.D., Taisuke IWAOKA, M.D.,
Teruhisa UMEDA, M.D., Junnosuke INOUE, M.D.,
Shinichiro HAMASAKI, M.D., Fumihiko MIURA, M.D.,
Yumiko FUJII, M.D., *and* Tatsuo SATO, M.D.

SUMMARY

In order to investigate the validity of angiotensin converting enzyme inhibition with captopril as a screening test for primary aldosteronism (PA), 50 mg of captopril were administered orally to 7 patients with PA, 17 with essential hypertension (EH), 5 with renovascular hypertension (RVH), 2 with renoparenchymal hypertension (RH) and 8 normal volunteers.

The plasma aldosterone concentration (PAC) was suppressed to less than 15 ng/dl in all of the EH, RVH and RH patients and normal subjects 90 min after administration of captopril, but not suppressed in 6 of 7 patients with PA. In addition, the plasma renin activity (PRA) was increased to greater than 1 ng/ml/h in 10 of 17 patients with EH and in all with RVH, RH and the normal controls, but to less than that in 6 of 7 PA and the remaining EH patients. The PAC to PRA ratio after captopril was greater than 20 in all patients with PA, while it remained below 20 in EH, RVH and RH patients and normal controls.

From these results, we conclude that the PAC to PRA ratio in the captopril administration test is a simple and useful tool to detect PA in hypertensive patients. In addition, the test has a great advantage in that it can be safely applied to outpatients with relatively severe hypertension.

Additional Indexing Words:

Primary aldosteronism Aldosterone to renin ratio Captopril

From the Department of Internal Medicine III, Kumamoto University Medical School, Kumamoto, Japan.

Supported by a Grant from the Ministry of Health and Welfare "Disorders of adrenal hormone" Research Committee, Japan, 1984.

Address for reprint: Shojiro Naomi, M.D., Department of Internal Medicine III, Kumamoto University Medical School, 1-1-1 Honjo, Kumamoto 860, Japan.

Received for publication August 27, 1984.

Manuscript revised December 28, 1984.

PPRIMARY aldosteronism (PA), described initially by Conn,¹⁾ is a syndrome caused by excessive production of aldosterone from an adrenal tumor. Hypertension, hypokalemic alkalosis, normal output of urinary 17-hydroxycortico-steroids and excessive production of aldosterone were original features of the syndrome. Later, the marked suppression of plasma renin activity (PRA), resulting from plasma volume expansion caused by mineralocorticoid excess, provided a potential tool to detect the surgically curable hypertension of PA.²⁾ However, extensive studies of PRA in hypertensive patients revealed that a considerable population of essential hypertensive (EH) patients showed suppressed PRA in the absence of excess levels of aldosterone. Furthermore, several cases of PA associated with high PRA have been reported,^{3),4)} mostly resulting from renal damage due to longstanding severe hypertension. Thus, the estimation of basal and or stimulated PRA is not adequate to establish the diagnosis of PA. Rather, it is necessary to demonstrate that the production of aldosterone is autonomous to establish the diagnosis of PA. For this purpose, maneuvers to suppress the renin-angiotensin-aldosterone system, such as high salt intake,⁵⁾ exogenous mineralocorticoid administration⁶⁾ and acute saline infusion⁷⁾ have been developed. Among these, the saline infusion test has been nominated as the most simple and reliable method. However, it is sometimes difficult to perform in the severely hypertensive patient. Lyon et al⁸⁾ have reported that the oral administration of captopril, a potent inhibitor of angiotensin I converting enzyme, might be an alternative method. Both captopril and saline infusion can lower circulating angiotensin II levels and decrease production of aldosterone in EH, renovascular (RVH) and renoparenchymal hypertension (RH). However, these have no effect on aldosterone production in patients with PA because of its independency from the renin angiotensin system.⁹⁾ We have previously reported¹⁰⁾ on the clinical usefulness of the captopril administration test in the diagnosis of PA. Those results were not conclusive because of an insufficient number of patients. The present study was undertaken to confirm the validity of this test to differentiate PA from other forms of hypertension.

PATIENTS AND METHODS

Seven patients with PA, 17 with EH, 5 with RVH, 2 with RH and 8 normal subjects were studied. All patients were admitted to our hospital and underwent detailed physical examination, routine blood tests, urinalysis and several hormonal profilings including PRA, plasma aldosterone concentration (PAC), urinary output of catecholamines, 17 KS and 17 OHCS.

All medications were discontinued after admission.

The diagnosis of PA was made by the presence of elevated PAC and subnormal PRA after a 1 mg/Kg intravenous injection of furosemide and 2 hours of ambulation. Subsequent adrenal venous sampling, scintiscans with ^{75}Se -sintadren with dexamethasone suppression, and high resolution computed tomography were performed. An unilateral adrenal adenoma was proven in all patients with PA. Therefore, no case of idiopathic hyperaldosteronism was included in the present study.

The diagnosis of RVH was made by rapid sequence intravenous pyelography, renal arteriography and PRA determination of renal venous samples. The diagnosis of RH was established by histological study of biopsied renal specimens. In 17 patients with EH, PA was excluded by normal basal PAC and suppressed PAC below 10 ng/dl after 7 days of sodium loading of 340 mEq/day. The 8 normal volunteers were healthy and had no history of hypertension, renal disease or endocrine disorders. Informed consent was obtained from all of patients and normal volunteers before being studied.

The hypertensive patients were studied after 7 hospital days on a daily sodium intake of 170 mEq, whereas normal subjects were studied without salt restriction. After an overnight fast and 30 min bed rest, the first blood sample was collected for basal PAC and PRA followed by oral administration of 50 mg captopril. The second sample blood was taken 90 min after the drug was given. PAC and PRA were determined by RIA as previously reported.¹⁰⁾ The data were statistically analyzed by Student's t-test. Grouped data were expressed as the mean $\pm$ SD.

RESULTS

Only one of 17 patients with EH showed a serum potassium level of less than 3.5 mEq/L. Six of 7 patients with PA had serum potassium levels of less than 3.5 mEq/L, but the one remaining patient had persistently normal serum potassium levels except for those during sodium loading. Serum potassium levels in all of RVH and RH patients were within normal limits (Table I).

PRA levels after stimulation with i.v. furosemide and upright posture in all patients are shown in Fig. 1. In all patients with PA and 2 patients with EH, PRA failed to be stimulated by the manipulation.

Individual captopril test data for each patient are given in Table II. In all EH, 3 of 5 RVH and 7 of 8 normal subjects, PAC before drug were less than 15 ng/dl and greater than 15 ng/dl in all of the PA and RH patients, while PAC levels at 90 min after drug administration were below

Table I. Clinical Data of Individual Subjects

Patient No.	Age (year)	Sex	MBP (mmHg)	Serum Na (mEq/L)	Serum K (mEq/L)	PRA (ng/ml/h)*		
						before	after	
EH	1	29	f	111	139	4.7	2.64	11.5
	2	34	m	141	142	3.5	2.28	8.51
	3	36	m	151	136	4.2	1.48	8.21
	4	36	f	109	141	3.7	0.25	0.64
	5	41	f	125	139	4.9	0.85	1.54
	6	43	m	126	137	4.1	0.52	1.32
	7	43	f	137	140	3.3	1.38	1.82
	8	47	m	110	141	3.7	2.73	5.72
	9	50	f	141	144	3.8	2.68	6.82
	10	51	f	122	147	3.7	0.60	1.28
	11	55	m	107	145	4.8	2.03	3.37
	12	56	m	109	140	4.5	0.80	4.53
	13	58	f	126	141	3.7	0.64	2.63
	14	59	m	112	140	4.5	0.59	2.11
	15	60	f	113	138	3.7	0.61	2.07
	16	61	m	143	143	3.7	2.64	11.5
	17	62	m	105	140	3.9	0.15	0.50
m±SD		48±10	123±15	141±3	4.0±0.5	1.23±0.88	3.93±3.12	
RVH	18	30	f	130	140	3.9	2.04	21.3
	19	35	m	115	140	4.4	1.23	5.20
	20	44	m	139	143	3.9	5.01	16.3
	21	53	m	126	142	4.5	1.86	7.40
	22	57	f	125	137	3.6	9.35	8.19
m±SD		44±10	127±8	140±2	4.1±0.3	3.90±3.02	11.6±6.1	
RH	23	33	f	150	143	4.8	1.63	2.54
	24	43	m	148	138	4.7	11.1	22.7
m±SD		38±5	149±1	141±3	4.8±0.1	6.37±4.74	12.6±10.1	
PA	25	27	m	119	145	2.8	0.13	0.69
	26	30	m	119	139	3.6	0.10	0.10
	27	35	f	132	140	2.8	0.10	0.10
	28	43	f	121	143	2.2	0.19	0.20
	29	46	m	150	143	2.7	0.10	0.45
	30	48	m	133	141	3.0	0.10	0.52
	31	56	f	118	141	3.2	0.22	0.30
m±SD		41±10	127±11	142±2	2.9±0.4†	0.13±0.05†	0.34±0.21†	

* PRA before and after furosemide 1 mg/Kg i.v. and upright posture.

† Significant difference ($p<0.01$) compared with EH and RVH.

15 ng/dl in all patients with EH, RVH, RH and normal controls and greater than 15 ng/dl in 6 of 7 patients with PA. The PRA after captopril increased to greater than 1 ng/ml/h in normal subjects and all of the RH and RVH

Fig. 1. The PAC to PRA ratios before and after 50 mg captopril administration in patients with PA, EH, RVH, RH and in normal subjects.

patients, whereas it was less than that in 7 of 17 EH patients and 6 of 7 patients with PA. The aldosterone to renin ratios before and after captopril are shown in Table II and Fig. 1. The ratios before captopril were greater than 20 in all the PA and 3 of 17 EH patients and one each of the RH and normal subjects. However, the ratios after captopril were never less than 20 in only the PA patients. This finding was unique to this group.

DISCUSSION

The present study has assessed the usefulness of the captopril administration test in the screening of PA and confirmed its diagnostic accuracy for the disease. When we take into account the ratio of PAC to PRA at 90 min after captopril administration, it seems to be superior to any of the other methods currently used for the purpose.

Various simplified procedures have been developed to improve the diagnostic accuracy of mineralocorticoid-induced hypertension. Low serum potassium is a convenient compass in the screening of PA especially for outpatients; however, its diagnostic accuracy is unsatisfactory. It is widely ac-

Table II. Results of Captopril Test

		PAC		PRA		PAC/PRA	
		0 min	90 min	0 min	90 min	0 min	90 min
EH	1	4.3	1.1	2.15	11.6	1.7	0.1
	2	9.2	4.3	3.85	8.11	2.4	0.5
	3	3.0	0.6	0.80	2.00	3.8	0.3
	4	7.5	2.8	0.16	0.23	46.9	12.2
	5	8.1	6.0	0.92	1.19	8.8	5.0
	6	9.8	3.2	1.02	0.79	9.6	4.1
	7	1.1	0.8	1.81	3.82	0.6	0.2
	8	3.3	1.8	2.42	9.08	1.4	0.2
	9	8.7	5.0	0.76	1.25	11.4	4.0
	10	8.5	5.9	0.66	0.59	12.9	10.6
	11	4.1	2.1	1.79	3.11	2.3	0.7
	12	10.0	7.0	0.44	0.98	22.7	7.1
	13	7.5	3.9	0.60	2.45	12.5	1.6
	14	5.3	3.9	0.46	0.50	11.5	7.8
	15	4.1	1.2	0.84	0.35	4.9	3.4
	16	4.9	6.5	2.60	15.1	1.9	0.4
	17	3.4	2.9	0.10	0.38	34.0	7.6
m±SD		6.1±2.7	3.5±2.0	1.28±1.01	2.20±2.53	11.1±12.3	3.8±3.8
RVH	18	8.6	5.7	1.70	25.3	5.1	0.2
	19	13.6	7.8	1.03	1.43	13.2	5.5
	20	16.4	12.4	4.26	61.4	3.8	0.2
	21	6.3	3.3	2.67	40.1	2.4	0.1
	22	20.2	11.7	0.82	9.40	24.6	1.2
m±SD		13.0±5.1	8.2±3.5	2.09±1.26	27.5±21.5	9.8±8.3	1.4±2.1
RH	23	19.9	7.9	1.50	2.44	13.3	3.2
	24	22.5	14.5	7.73	30.8	2.9	0.5
m±SD		21.2±1.3	11.2±3.3	4.62±3.12	16.6±14.8	8.1±5.2	1.9±1.4
PA	25	25.2	32.9	1.77	1.32	21.5	24.9
	26	18.6	26.8	0.10	0.10	186	268
	27	22.4	23.5	0.10	0.10	224	235
	28	20.2	26.3	0.93	0.15	21.9	175
	29	25.0	11.3	0.41	0.46	60.9	24.6
	30	19.3	16.8	0.10	0.10	193	168
	31	45.6	37.9	0.15	0.15	304	253
m±SD		25.2±8.7*	25.1±8.4*	0.42±0.41#†	0.34±0.42#†	144±102*	164±94.6*
NC (n=8)							
m±SD		7.0±4.3	4.1±3.0	1.03±0.73	6.59±9.02	10.8±13.5	1.3±0.8

* Significant difference (p<0.01) compared with EH, RVH and NC.

Significant difference (p<0.01) compared with RVH.

† Significant difference (p<0.05) compared with EH and NC.

cepted that a more dependable marker to detect PA¹¹⁾ is the suppression of PRA after i.v. furosemide followed by 1 or 2 hours of upright posture, but we failed to distinguish the disease completely from so-called low renin EH. Moreover, some of our female patients were unable to maintain upright posture for 2 hours after furosemide administration. Therefore, a more adequate diagnostic test for PA is needed.

Recently, Lyon et al⁸⁾ have reported on the usefulness of captopril as an alternative tool to diagnose PA. It has been noticed that the drug has no effect on aldosterone production in patients with PA because of the autonomous production of the steroid. We previously reported that the captopril test was a simple and safe test to evaluate the role of the renin angiotensin system in hypertensive patients.¹⁰⁾ Therefore, we concentrated on the usefulness of the drug for the diagnosis of PA. As stated by Lyon et al, 6 of our 7 patients with PA also showed a PAC of greater than 15 ng/dl at 90 min after the administration of captopril, while patients with other forms of hypertension did not. However, we still could not diagnose as PA one patient with PA, proven to have an aldosteronoma by operation, using only this criterion. On the other hand, captopril increases PRA by decreasing the negative feedback of angiotensin II in patients with EH, but has little effect on PRA in patients with PA. However, in the present study, 7 of 17 patients with EH failed to increase their PRA above 1 ng/ml/h after the administration of captopril, and thus might be classified in the low renin group of EH. Therefore, the response of PRA itself to the drug cannot be a reasonable criterion. Lyon et al⁸⁾ also proposed the use of an aldosterone to renin ratio of 50 to separate PA from other forms of hypertension. When we used a ratio of 50, 2 of our PA patients had to be grouped in EH. Therefore, it seems a reasonable criterion to use a ratio of 20 in our study because all our patients with PA showed ratios greater than that and none of the patients with other forms of hypertension including EH, RVH and RH had ratios below 20. Further expanded studies will be needed to decide on the proper ratio to be set as the borderline to separate PA patients from others.

It is widely accepted that the lack of suppression of PAC by a saline infusion might be a most reliable diagnostic criterion for PA. However, the test is at times not easily performed in patients with severe hypertension because of the acute loading of 2 liters of saline. In contrast, the captopril test has no marked side effects and can be performed within 2 hours. Therefore, the captopril test might be a convenient, less harmful and more accurate test for the diagnosis of PA. In addition, the effect of sodium intake on the PAC to PRA ratio after captopril is under investigation in an attempt to apply the test to outpatients without the necessity of employing dietary sodium

manipulation.

REFERENCES

1. Conn JW: Primary aldosteronism: A new clinical syndrome. *J Clin Lab Med* **45**: 6, 1955
2. Conn JW, Rovner DR, Cohen EL, Bookstein JJ, Cerney JC, Lucas CP: Preoperative diagnosis of primary aldosteronism. *Arch Intern Med* **123**: 113, 1969
3. Baglin A, Weiss Y, Saftir M, Milliez P: Hyperaldosteronism primaire avec Hypertension Maligne. *Le Nouvelle Presse Medicale* **2**: 5, 1973
4. Iwaoka T, Umeda T, Sato T, Katsuragi S, Takeuchi T: High plasma renin activity in primary aldosteronism with malignant hypertension. A case report. *Jpn Heart J* **21**: 423, 1980
5. Collins RD, Weinberger MH, Dowdy AJ, Nokes GW, Gonzales CM, Luetscher JA: Abnormally sustained aldosterone secretion during salt loading in patients with various forms of benign hypertension: relation to plasma renin activity. *J Clin Invest* **49**: 1415, 1970
6. Salton DE Jr, Schambelan M, Biglieri EG: Stimulation and suppression of aldosterone secretion in patients with aldosterone-producing adenoma. *J Clin Endocrinol Metab* **29**: 239, 1969
7. Kem DC, Weinberger MH, Mayes DM, Nugent CA: Saline suppression of plasma aldosterone in hypertension. *Arch Intern Med* **128**: 380, 1971
8. Lyon DF, Kem DC, Brown RD, Hanson CS, Carollo ML: Single dose captopril as a diagnostic test for primary aldosteronism. *J Clin Endocrinol Metab* **57**: 892, 1983
9. Luderer DF, Demers LM, Hrrison TS, Hayes AH Jr: Converting enzyme inhibition with captopril in patients with hyperaldosteronism. *Clin Pharmacol Ther* **31**: 305, 1982
10. Iwaoka T: Clinical evaluation of renin angiotensin system in hypertensive patients with oral angiotensin converting enzyme inhibitor. *Kumamoto Med J* **36**: 79, 1983
11. Weinberger MH, Grim CE, Hollifield JW, Kem DC, Ganguly A, Kramer NJ, Yune HY, Wellman H, Donohue JP: Primary aldosteronism: diagnosis, localization, and treatment. *Ann Int Med* **90**: 386, 1979