Effects of San-Huang-Hsieh-Hsin-Tang on Sympathetic Activity, Plasma Renin, and Plasma Aldosterone

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ABSTRACT

San-Huang-Hsieh-Hsin-Tang, an ancient Chinese remedy for gastrointestinal disorders, was also found to lower blood pressure. The authors therefore investigated the effects of this substance on sympathetic activity, plasma renin, and plasma aldosterone. Sympathetic activity and plasma renin activity, but not plasma aldosterone levels, were significantly reduced with treatment. The depressed plasma renin activity could be secondary to depressed sympathetic activity. The discrepancy between plasma renin activity and plasma aldosterone levels, which is also found with beta-blockers, could be explained by the following sequence: decreased renin → decreased aldosterone → increased serum potassium → recovery of aldosterone.

INTRODUCTION

We have found that San-Huang-Hsieh-Hsin-Tang (ST), an ancient Chinese remedy for "epigastric fullness, flushing-up, restlessness, constipation, and a hard pulse," can be used to treat essential hypertension.[1,2] In a dosage of 500 mg TID, ST significantly lowered ($P < 0.001$) blood pressure from mean ($\pm$SD) values of $167 \pm 15/108 \pm 10$ mmHg to $140 \pm 16/88 \pm 8$ mmHg in 30 patients. It had no apparent adverse effects on symptoms, signs, liver function tests (SGOT, SGPT, alkaline phosphatase, bilirubin, globulin, and albumin), renal function tests (BUN, serum creatinine), electrolyte balances, fasting blood sugar, blood, urine, and stool routine examinations, ECG, or chest roentgenographic findings. The two side effects reported

were slightly increased bowel movement and deep-yellow urine, neither of which caused distress; both were reversible by discontinuing the treatment.

Hemodynamic studies showed that ST significantly decreased the hyperdynamic states of the cardiovascular system (H.-C. Chen et al, unpublished data, 1985). To clarify the mechanism of ST in essential hypertension, we investigated the effects of ST on sympathetic activity, plasma renin activity, and plasma aldosterone levels.

MATERIALS AND METHODS

Preparation of the Test Drug

The preparation consisted of coarse powders of Rheum *officinale* Baillon (*Polygonaceae*), Coptis *chinensis* Wallich (*Ranunculaceae*), and Scutellaria *baicalensis* George (*Labiatae*), in the ratio of 3:2:1. The mixture (1 kg) was immersed in 5,000 ml of 95% alcohol at room temperature for three days and then extracted in a water bath at a temperature below 80 °C several times until the solution was clear. The extracted solution was evaporated and concentrated in a rotary vacuum evaporator at a temperature below 60 °C. The sample was obtained by lyophilizing the concentrated extract and then pulverizing it through a No. 80 mesh. Finally, the powder was poured into capsules (500 mg per capsule).

Patients

Patients with essential hypertension of WHO grades I and II[3] were selected for the study. Excluded were patients with other specific conditions (eg, bronchial asthma, hepatitis), patients who had taken any medication in the preceding four weeks, and pregnant women.

Procedures

The study encompassed four weeks. During the first week, patients were given placebo in capsules identical to those used for the active drug. Then they were given 500 mg of ST TID for two weeks, followed by placebo for the final week.

Before a patient received placebo (visits 1, 3) or active drug (visit 2), and at the end of the study (visit 4), sympathetic activity, plasma renin activity, and plasma aldosterone levels were determined. Sympathetic activity was assessed by means of (1) alleviation of the sympathetic symptoms present before treatment, (2) hemodynamic changes (heart rate, blood pressure) during orthostasis, and (3) plasma norepinephrine concentration.[4-6] Renin activity and aldosterone levels were evaluated by measuring these substances in the plasma.

On each measurement day, the patients were asked to eat a light breakfast without coffee and to abstain from smoking before coming to our laboratory. They arrived about 10 AM. The room temperature was kept constant.

An intravenous indwelling catheter was inserted, and patients were asked to sit upright to achieve steady state (indicated by heart rate of less than 80 beats/min and varying by no more than 4 beats/min). After steady state was obtained, blood samples were drawn for assays of plasma norepinephrine,[7] plasma renin,[8] and plasma aldosterone.[9] A 24-hour urine collection was also made, and an aliquot was taken for measurement of

Table I. Subjective improvement of sympathetic symptoms in 30 patients treated with ST.

Symptoms	Frequency Before Treatment		Response After Two Weeks of ST				
	No. of Patients	Percent	Remarkably Effective	Effective	Slightly Effective	Not Effective	Percent Efficacy
Palpitations	25	83	3	14	6	2	92
Chest pain	15	50	1	8	4	2	87
Flushing	19	63	8	9	1	1	95
Headache	14	47	1	4	8	1	93
Nervousness	16	53	1	2	8	5	69
Constipation	8	27	5	2	1	0	100

sodium and potassium. If the 24-hour urinary potassium excretion was less than 40 mEq, the collection was considered to be incomplete.

Orthostatic studies were performed next. After each patient had rested supine to achieve steady state, determinations were made with the patient recumbent, standing, and then recumbent again, at two-minute intervals for about 20 minutes. Changes of posture were made by the patient with as little expenditure of energy as possible. An effort was made to have each patient mentally and physically relaxed.

Patients were also queried about subjective improvement while taking ST.

Results were analyzed statistically using paired Student's *t* test to compare intergroup differences.

RESULTS

All of the sympathetic symptoms improved after treatment with ST (Table I). This finding might imply that the compound lowered basal sympathetic activity. Blood pressure and heart rate responses to orthostatic stresses were significantly dulled ($P < 0.05$) by ST but not by placebo (Table II and figure).

Plasma norepinephrine and plasma renin concentrations were not affected after the first week of placebo, but they were significantly depressed ($P < 0.05$) after two weeks of ST. After the final week of placebo, these values rose considerably. Plasma aldosterone level was not significantly altered by either ST or placebo.

DISCUSSION

From the foregoing results, we might conclude that ST significantly lowered both sympathetic activity and plasma renin activity but only marginally decreased plasma aldosterone levels.

We could not tell, however, whether the antirenin effect was secondary to an

Table II. Effects of ST on orthostatic heart rate and blood pressure in 30 patients (changes during standing).

	Visit			
	1	2	3	4
Systolic blood pressure (mmHg)				
Mean	−1.0	−1.1	−3.4*	−2.5
SD	5.6	5.4	4.9	5.1
Diastolic blood pressure (mmHg)				
Mean	3.6	3.5	2.0*	3.1
SD	3.7	3.6	3.4	3.5
Heart rate (beats/min)				
Mean	14.0	14.0	11.0†	13.0‡
SD	3.0	3.0	2.8	±2.9

* $P < 0.05$ (visit 2–visit 3).
† $P < 0.001$ (visit 2–visit 3).
‡ $P < 0.01$ (visit 3–visit 4).

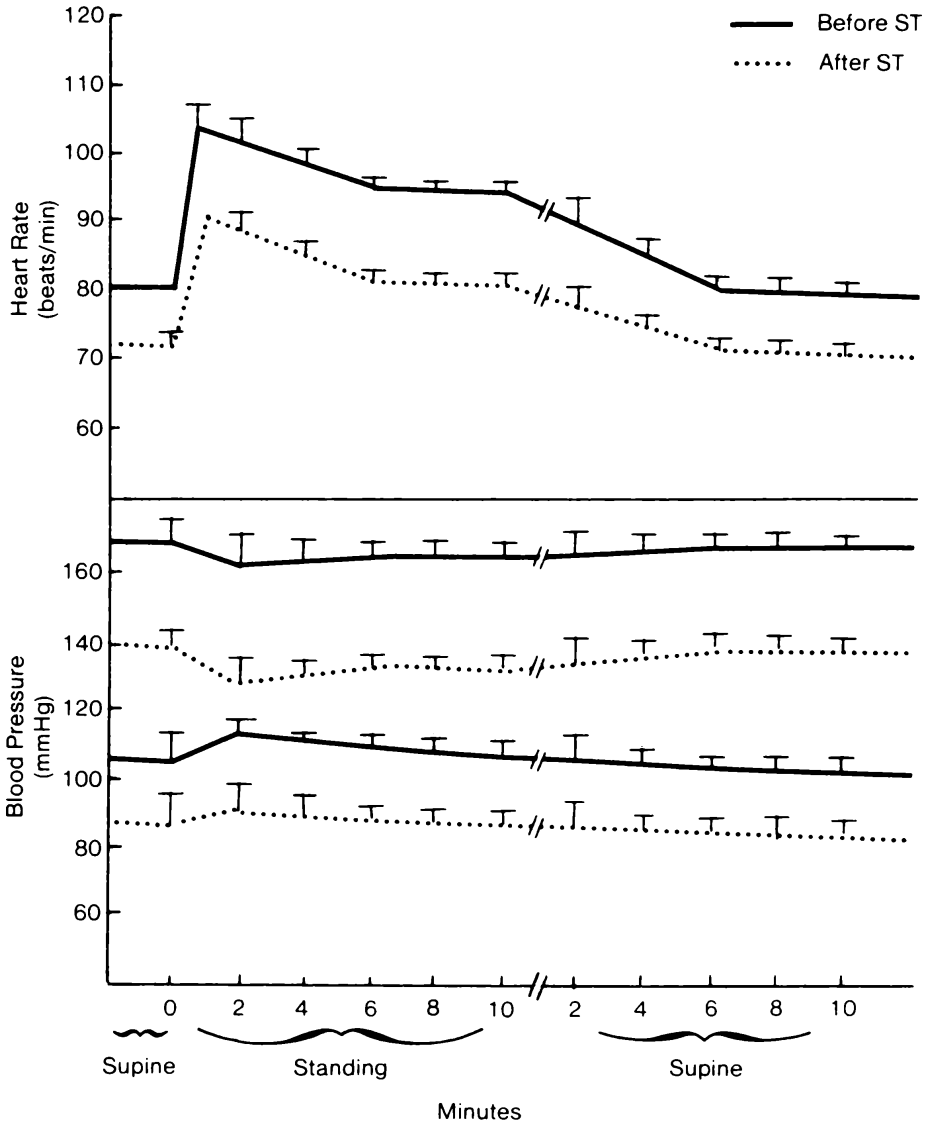

Figure. Blood pressure and heart rate changes (mean, ± SE) during orthostasis.

antisympathetic effect or if ST had a direct antirenin effect.[10] To elucidate this point, we denervated the renal nerves in rats by stripping the perivascular tissue. After renal denervation, the antirenin effect of ST was completely lost. Although the renal nerves are mainly sympathetic, some parasympathetic fibers are also present. However, any parasympathetic fibers in the renal nerves are distributed to the smooth muscle in the renal pelvis and the proximal portion of the ureter. Juxtaglomerular cells receive only sympathetic fibers.[11] Therefore, we might conclude that the antirenin effect of ST was secondary to the antisympathetic effect of ST.

An agent that inhibits renin should also inhibit aldosterone. In this study, plasma aldosterone levels were only marginally lowered. This discrepancy, which is also found with beta-blockers, could be explained by the following sequence: depressed renin → depressed

Table III. Effects of ST on plasma norepinephrine, plasma renin, and plasma aldosterone in 30 patients.

	Visit			
	1	2	3	4
Plasma norepinephrine (pmol/min)				
Mean	1.23	1.22	1.01*	1.17*
SD	0.37	0.36	0.35	0.34
Plasma renin activity (pmol/ml/hr)				
Mean	2.32	2.28	1.85†	2.17*
SD	0.79	0.75	0.76	0.76
Plasma aldosterone (pmol %)				
Mean	31.29	31.32	29.94	31.50
SD	5.60	5.44	5.45	5.41

* $P < 0.05$ (visit 2–visit 3; visit 3–visit 4).
† $P < 0.01$ (visit 2–visit 3).

aldosterone → elevated serum potassium → recovery of aldosterone.

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REFERENCES

1. Chen HC, Hsieh MT, Tsai HY, et al. Studies on the San-Huang-Hsieh-Hsin-Tang in the treatment of essential hypertension. *J Formosan Med Assoc* 1984; 83:340–346.
2. Chang HH. *Comparison between San-Huang-Hsieh-Hsin-Tang and beta-blocker + diuretic + vasodilator,* thesis. Institute of Chinese Pharmaceutical Sciences, China Medical College, Taiwan, 1984.
3. World Health Organization. Arterial hypertension. *WHO Tech Rep Ser* 1972; 231:20.
4. Peter SS. The sympathetic nervous system and hypertension. In: Sleight P, Jones JV, eds. *Cardiology*. London: William Heinemann Medical Books, 1983:147–155.
5. Birkenhanger W. The sympathetic system and hypertension. In: Laragh JH,

Buhler FR, Seldin DW, eds. *Frontiers in hypertension research*. New York: Springer-Verlag, 1981:283–329.

6. Kuchel O. The autonomic nervous system and blood pressure regulation in human hypertension. In: Genest J, Kuchel O, Hamet P, Cantin M, eds. *Hypertension*. New York: McGraw-Hill, 1983:140–163.
7. Renzini V, Brunori CA, Valori C. A sensitive and specific method for determination of noradrenaline and adrenaline in human plasma. *Clin Chim Acta* 1970; 30:340–346.
8. Sealey JE, Laragh JH, Banes GJ, et al. The measurement of plasma renin activity in man. In: Laragh JH, ed. *Hypertension manual*. New York: Springer-Verlag, 1974:621–641.
9. Buhler FR, Sealey JE, Laragh JH. Radioimmunoassay of plasma aldosterone. In: Laragh JH, ed. *Hypertension manual*. New York: Springer-Verlag, 1974:655–673.
10. Freeman RH, Davis JO. Factors controlling renin secretion and metabolism. In: Genest J, Kuchel O, Hamet P, Cantin M, eds. *Hypertension*. New York: McGraw-Hill, 1983:225–250.
11. Kuntz A. Innervation of the adrenal glands and the kidneys. In: Netter FH, ed. *The CIBA collection of medical illustration*. Vol. 1. *Nervous system*. New York: CIBA, 1972:97–98.