Clinical Trial of Suanzaorentang in the Treatment of Insomnia

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ABSTRACT

The hypnotic effect of suanzaorentang, an ancient Chinese remedy for insomnia, was studied in 60 patients with sleep disorders. After receiving placebo for one week, patients ingested capsules containing 1 gm of suanzaorentang each night, 30 minutes before bedtime, for two weeks. Treatment was followed by another week of placebo administration. Each morning during the study, patients completed questionnaires relating to their sleep the night before and to their ability to function during the previous day. Analysis of the responses showed statistically significant improvements ($P < 0.001$) in all ratings of sleep quality and well-being during active treatment compared with both placebo periods. Laboratory tests performed before and after treatment with suanzaorentang showed no alterations in any test value. No side effects were noted. We conclude from these results that the compound merits further extensive investigation.

INTRODUCTION

Suanzaorentang is an ancient Chinese remedy for insomnia. Its formula was originally described in Chin-Kuei-Yao-Lueh[1] about 2,000 years ago. Modern Chinese physicians still use it for the treatment of insomnia, although, until now, there has been no scientific study of this compound.

We have tested different combinations and preparations of the components in rats to get the most sedative effect. The only component showing any sedative effect was Zizyphi seed; however, this effect was not nearly as strong as that of suanzaorentang.

A modified suanzaorentang compound was specially prepared by the Institute of Chinese Pharmaceutical Sciences and

given to patients with insomnia in a clinical trial to assess the hypnotic effects of this preparation.

MATERIALS AND METHODS

Preparation of Suanzaorentang

The preparation consisted of coarse powders of Zizyphus *spinosus* Hu (Rhamnaceae), Poria *cocos* (Schw.) Wolf (Polyporaceae), Ligusticum *chuanxiong* Hort (Umbelliferae), Anemarrhena *asphodeloides* Bunge (Liliaceae), and Glycyrrhiza *uralensis* Fischer et DC. (Leguminosae), in the ratio of 7.5:2:2:1:1.

The mixture (1 kg) was immersed in 5,000 ml of 95% alcohol at room temperature for three days and then extracted in 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.

Patients

Patients complaining of reduced ability to sleep and reduced daytime alertness were selected as subjects for the study. Excluded were patients with other specific conditions (eg, heart failure, respiratory failure, hypertension), patients who had taken any medication in the preceding four weeks, and pregnant women.

Treatment and Data Collection

Patients accepted into the study were given placebo capsules containing 1 gm of lactose. They were to take one tablet 30 minutes before bedtime during the first week. Suanzaorentang, 1 gm 30 minutes before bedtime, was prescribed for the next two-week period, after which they were given placebo capsules for one more week.

Within the first two days of the first week, a battery of laboratory tests was performed to rule out any other specific conditions and to assess the safety of suanzaorentang. Determinations were made of renal function (blood urea nitrogen and serum creatinine), liver function tests (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, lactate dehydrogenase, albumin, globulin, and bilirubin), serum electrolyte balance (potassium, sodium, chloride, and calcium), serum cholesterol-triglyceride concentrations, and vital signs, including blood pressure and heart rate. Routine examinations were made of blood, urine, and stool, and a chest roentgenogram was made. These tests were repeated after the two-week treatment with suanzaorentang.

Questionnaires for assessing insomnia were given to each patient to be completed within 30 minutes of arising in the morning. The forms contained questions concerning sleep onset latency and number of intercurrent awakenings. Subjects were also asked, "How well did you sleep last night?" and "How well did you function during the day?" They were to record the answers using a seven-point scale relative to their usual state before entering the study (1 = much worse, 4 = exactly the same, 7 = much better).

RESULTS

Sixty patients (30 men and 30 women) between the ages of 22 and 49 years completed the study. The duration of sleep problems ranged from four months to five years. Sleep onset was a problem for 87% of the subjects, and sleep maintenance was a problem for 64%. Symptoms associated with insomnia included palpitations, nervousness, neck stiffness, perspiration, and low-back pain.

The table shows that during treatment with suanzaorentang, all sleep measures were significantly improved ($P < 0.001$); those symptoms accompanying insomnia abated. One week after the compound was withdrawn, however, all sleep measures deteriorated significantly.

No side effects were observed during treatment with suanzaorentang. All laboratory tests and other examinations were unaltered after two weeks' administration of the compound.

DISCUSSION

Insomnia is among the most frequent disorders leading people to seek help. Rational treatment of this problem is directed toward the underlying causes. Unfortunately, most causes of insomnia are idiopathic, and physicians resort to prescribing hypnotics.

Some Chinese physicians use suanzaorentang to treat patients with insomnia. The Zizyphi seed in this formula has been reported to have sedative effects,[2,3] and we found it to be the only component in this compound that does have a sedative effect. The only modern clinical study on the formula is that of Ohwada et al.[4] They studied the electroencephalographic effect of suanzaorentang and found that this preparation did not affect the rapid eye movement period of sleep. In our clinical trial, we found that suanzaorentang improved sleep quality and the feeling of daytime well-being without

Table. Effects of suanzaorentang on sleep (mean ± SD).

Variable	No. of Patients	Treatment Period		
		Placebo	Suanzaorentang	Placebo
Sleep latency (min)	52	62 ± 14*	25 ± 10*	45 ± 12
Sleep time (hr)	60	4.9 ± 0.7*	7.2 ± 0.6*	5.4 ± 0.7
No. of intermittent awakenings	38	4.2 ± 1.1*	2.3 ± 0.6*	4.4 ± 1.2
How well slept†	60	4.2 ± 0.5*	5.9 ± 0.4*	4.1 ± 0.4
How felt on awakening†	60	4.1 ± 0.3*	5.5 ± 0.5*	4.0 ± 0.3

* Difference between treatments significant ($P < 0.001$; Student's t test).
† Based on seven-point scale.

causing any apparent side effects. When compared with diazepam, suanzaorentang was found not to cause daytime drowsiness.

Suanzaorentang also improved the accompanying symptoms of insomnia, such as palpitations, perspiration, nervousness, neck stiffness, restlessness, and lower-back pain. All of these symptoms are frequently observed as well in patients with anxiety, postmenopausal syndrome, and increased sympathetic activity. Therefore, suanzaorentang may also be effective in the treatment of these conditions.

One further finding is of interest. In rats we used the combination of levodopa and benserazide to cause locomotor stimulation; stereotyped movements including head shaking, forepaw padding and jumping; and autonomic symptoms including salivation, exophthalmos, and piloerection.[5] These symptoms were reduced by administering suanzaorentang, implying that this agent may reduce catecholaminergic activity.

Our clinical results with suanzaorentang suggest that further investigation of this compound is warranted.

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REFERENCES

1. Chang TC. Chin kue yadlueh. In: Wang YC. *Chin kue analysis*. Chue-En Co. 1981:265.

2. Watanabe J, Sarto H, Takagi K. Pharmacological studies of Zizyphus seeds. *Jpn J Pharmacol* 1973; 23:563–565.

3. Shibata M, Fukushima M. Acute toxicity and sedative action of Zizyphus seeds. *Yakugaku Zasshi* 1975; 95:465–468.

4. Ohwada S, Ohama N, Shimada T, et al. Effect of suanzaorentang for healthy young adults on sleep EEG. *Proc Symp WAKAN-YAKU* 1983; 16:235–239.

5. Hsieh MT. The involvement of monoaminergic and GABAergic systems in locomotor inhibitor produced by clobazam and diazepam in rats. *Int J Clin Pharmacol Ther Toxicol* 1982; 20(5): 227–235.