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Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang) as Treatment of Painful Muscle Cramps in Patients with Lumbar Spinal Stenosis and Its Minimum Effective Dose

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Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang) is a Kampo medicine, which is known to be effective against muscle cramps as well as crampy pain in the gastrointestinal smooth muscle and skeletal muscle. However, glycyrrhizin in this medicine also causes adverse drug reactions such as hypokalemia, hypertension, and edema. We analyzed the therapeutic efficacy of Shakuyaku-kanzo-to for painful muscle cramps associated with lumbar spinal stenosis and clarified its minimum effective dose.

58 patients with lumbar spinal stenosis and painful muscle cramps were included. We evaluated the therapeutic efficacy of Shakuyaku-kanzo-to (n=16) comparing with eperisone hydrochloride (n=14). We then examined the minimum effective dose of Shakuyaku-kanzo-to in the remaining 28 patients.

Shakuyaku-kanzo-to reduced the frequency of painful muscle cramps to less than 50% in 13 of 16 patients. However, eperisone hydrochloride reduced it to the same level in 4 of 14 patients. The onset of the maximum therapeutic effect of Shakuyaku-kanzo-to was less than 3 days from the start of treatment in 11 of 15 patients. Regarding the minimum effective dose for painful muscle cramps, 2.5 g of Shakuyaku-kanzo-to used as needed had a therapeutic effect that was equivalent to the regular use of 7.5 g/day (given in divided doses three times daily).

Our data show that Shakuyaku-kanzo-to is effective for painful muscle cramps associated with lumbar spinal stenosis. The dosage of 2.5 g of Shakuyaku-kanzo-to as needed had a therapeutic effect that was equal to the regular use of 7.5 g/day.

INTRODUCTION

Many patients visiting pain clinics with low back pain or leg pain actually suffer from lumbar spinal stenosis, which often involves painful muscle cramps. Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang), which is an herbal medicine (Kampo medicine) that has been used for a very long time in traditional medicine in East Asia, is known to be effective for painful muscle cramps as well as crampy pain in the gastrointestinal smooth muscle and in skeletal muscle. Shakuyaku-kanzo-to consists of two herbs: *P. lactiflora* and *Glycyrrhiza*. These two herbs contain paeoniflorin, a monoterpene glycoside, and glycyrrhizin, a triterpene glycoside, respectively. The application of the combination of paeoniflorin and glycyrrhizin reportedly produced a muscle relaxant effect in mouse phrenic nerve specimens as a result of the synergistic action of the two compounds (1). Indeed, Shakuyaku-kanzo-to effectively relieves painful muscle cramps associated with lumbar spinal stenosis, which is a common symptom occurring in outpatients in pain clinics, and is widely used in their treatment (2, 3, 10). Glycyrrhizin, however, is known to cause hypokalemia, hypertension, and edema as pharmacological adverse drug reactions (14). Administration of the minimum effective dose is thus preferable.

In this study, we compared the effectiveness of Shakuyaku-kanzo-to for painful muscle cramps associated with lumbar spinal stenosis with that of eperisone hydrochloride, which is widely prescribed as muscle relaxant

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and is often administered in case of muscle cramps. Then we determined the minimum effective dose of Shakuyaku-kanzo-to.

MATERIALS AND METHODS

Patients

Subjects in this study included 58 patients with lumbar spinal stenosis and painful muscle cramps. These patients were assessed for eligibility for our study and had no electrolyte disturbances or muscle diseases. Table I shows the demographic features of the patients. The patients were randomized, but not blinded, to 3 groups. Sixteen of them were assigned to evaluate the therapeutic efficacy of Shakuyaku-kanzo-to for muscle cramps, 14 were for the therapeutic efficacy of eperisone hydrochloride for muscle cramps and 28 patients comprised the group analyzed for the minimum effective dose of Shakuyaku-kanzo-to (Figure 1).

This study was performed according to the "Ethical Guideline for Clinical Study" of the Ministry of Health, Labour and Welfare of Japan. It was approved by the Ethical Committee of the Kobe University Graduate School of Medicine (permission number 1448) and informed consents were obtained from all the patients. All patients and their families gave informed consent for inclusion in the study.

Table I. Demographic features of the patients enrolled in our study

	Analysis of therapeutic effect group	**Analysis of therapeutic effect of eperisone hydrochloride group**	**Analysis of minimum effective dose group**
N	16	14	28
Age mean±SD (year)	67.9±8.6	66.7±9.5	68.1±12.3
Sex (M/F)	9/7	7/7	14/14
Height (cm)	158.6±8.8	159.7±7.9	160.0±9.6
Weight (kg)	61.5±9.3	60.8±9.0	62.1±8.9
Symptom duration mean (range)(months)	17.2 (3-48)	16.8 (4-48)	17.4 (4-36)

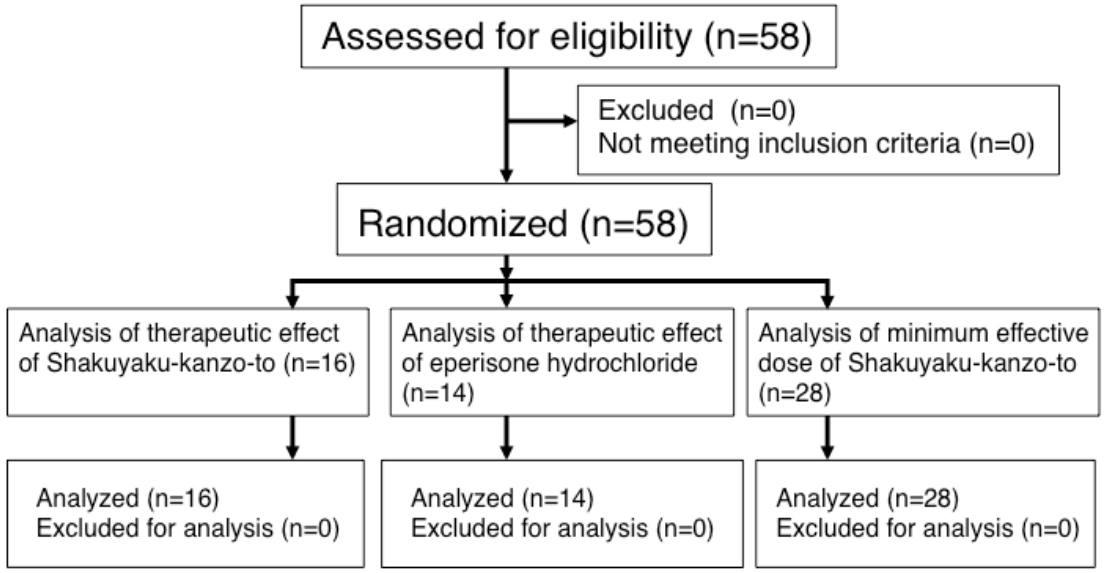

Figure 1. Consort diagram of patient flow

Method of evaluating the therapeutic effect

The therapeutic effectiveness of Shakuyaku-kanzo-to and eperisone hydrochloride was determined at 2 weeks after the start of medication by comparing the frequency of muscle cramps after treatment with the frequency before treatment as follows. A complete response was defined as a reduction in frequency to less than

25% of the original frequency; a partial response, from 25% to 50%; a minor response, from 50% to 75%; and no response, 75% or higher. The therapeutic effect, as based on this classification, was then scored as follows: 3 points for a complete response, 2 points for a partial response, 1 point for a minor response, 0 points for no response, and -1 point for a dropout. The scores for each group were calculated and compared.

Analysis of the therapeutic effect of Shakuyaku-kanzo-to for muscle cramps

This part of the analysis evaluated 16 patients, 9 men and 7 women, in the age range 55-80 years (mean age ± SD: 67.94 ± 8.61 years). Patients were administered Shakuyaku-kanzo-to extract granules (No. TJ-68, Tsumura Co. Ltd., Tokyo, Japan: http://www.tsumura.co.jp/english/products/pi/JPR_T068.pdf) three times daily, for a total of 7.5 g/day, for 2 weeks.

The patients were asked how many days they needed to obtain the maximum therapeutic effect and were classified into four groups: less than 3 days, 3-7 days, 7-14 days, and 14 days or more. We then analyzed the onset of the therapeutic effect of Shakuyaku-kanzo-to.

Evaluation of adverse drug reactions to Shakuyaku-kanzo-to

The patients were properly informed before treatment about the possible adverse drug reactions of Shakuyaku-kanzo-to and were instructed to stop taking the Kampo medicine when they experienced any abnormality. The patients were also instructed to consult a doctor in our pain clinic once every 2 weeks for measurement of their blood pressure and recording of adverse drug reactions, if any. Routine blood tests were performed 2 and 12 weeks after the initiation of the medication, or whenever clinically judged necessary.

Determination of minimum effective dose of Shakuyaku-kanzo-to

In the analysis of the minimum effective dose of the medicine, 28 patients, 14 men and 14 women, in the age range 57-86 years (mean age ± SD: 68.04 ± 10.33 years), were studied.

The treatment started with a total dose of 7.5 g/day for all patients, and at 2 weeks after the initiation, patients were instructed that they could change their dosage depending on their symptom, that is, when the frequency of the muscle cramps decreased, they could reduce the dosage. Then at 12 weeks after the initiation of the medication, we found 5 patients still took 7.5 g/day, 5 patients took 5g/day , 8 patients 2.5 g/day, 5 patients 2.5 g as needed and 5 patients finished (completed treatment).

We then compared these five groups for the therapeutic effect at 12 weeks since the first administration of the drug.

Statistical Analysis

Statistical analyses were performed with the R software (8). The relationship between therapeutic effect and the time required for the maximum therapeutic effect was analyzed by Pearson's chi-square test. Differences in response scores were tested by one-way ANOVA followed by Tukey's post-hoc test. A P value < 0.05 was regarded as significant.

RESULTS

Therapeutic effect of Shakuyaku-kanzo-to on muscle cramps

After 2 weeks of administration, we evaluated the change in the frequency of painful muscle cramps. With Shakuyaku-kanzo-to administration, 8 patients had a complete response; 6 patients had a partial response; 1 patient had a minor response; and 1 patient had no response, whereas with eperisone hydrochloride, only 1 patient had a complete response; 3 had a partial; 3 had a minor and residual 7 had no response (Table II). Shakuyaku-kanzo-to therefore reduced the frequency of painful muscle cramps to 50% or less of the original frequency in more than 87% of the patients (14 of 16).

Table II. Improvement in painful muscle cramps after Shakuyaku-kanzo-to treatment and eperisone hydrochloride

Therapeutic effect	No.(%) of patients of Shakuyaku-kanzo-to	No.(%) of patients of Eperisone hydrochloride
Complete response	8 (50.0)	1 (7.14)
Partial response	6 (37.5)	3 (21.43)
Minor response	1 (6.25)	3 (21.43)
No response	1 (6.25)	7 (50)
Total	16 (100)	14 (100)

Time required for the maximum therapeutic effect

We investigated how many days were needed from the start of administration to achieve the maximum therapeutic effect. For 11 patients, fewer than 3 days were required; for 2 patients, 3-7 days; for 1 patient, 7-14 days; and for 1 patient, more than 14 days (Figure 2). In more than half of the 16 patients, therefore, the maximum therapeutic effects occurred within less than 3 days.

The chi-square test showed an association between therapeutic effect and time required for the maximum therapeutic effect (χ^2 = 33.01, $P < 0.001$).

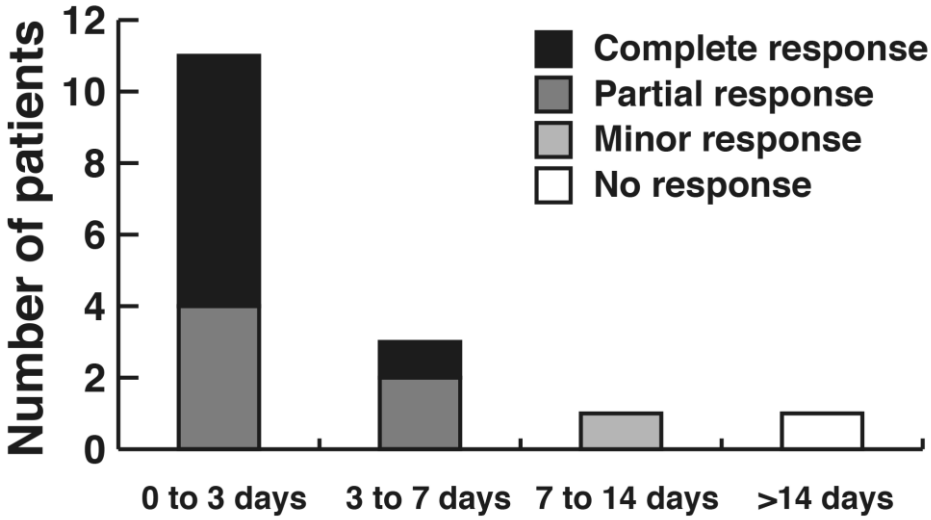

Figure 2. Time required for the maximum therapeutic effect

We classified 16 patients based on the days that were needed from the start of administration to achieve the maximum therapeutic effect.

Minimum effective dose of Shakuyaku-kanzo-to

We interviewed patients at 12 weeks after the treatment started. Symptoms were alleviated in 26 of 28 patients, with dosages at that time as follows: 7.5 g/day for 5 patients, 5 g/day for 5 patients, 2.5 g/day for 8 patients, 2.5 g as needed for 5 patients, and completed treatment for 3 patients.

We then calculated the patients' response scores according to the frequency of muscle cramps. The scores of the group that had completed treatment were significantly lower than those of all other groups. No significant difference was observed among any other groups (Figure 3).

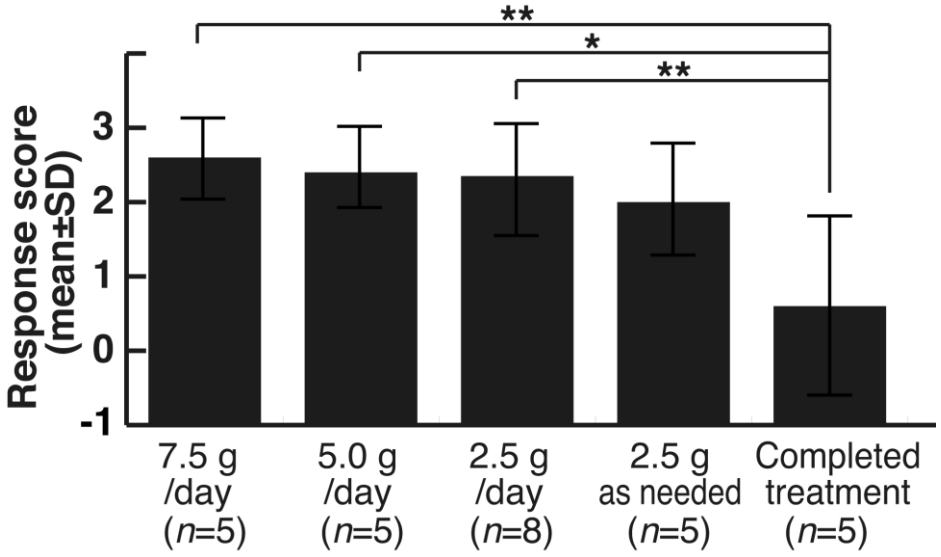

Figure 3. Dosages and responses to painful muscle cramps

Response scores were defined as a complete response: 3 points; partial response: 2 points; minor response: 1 point; no response: 0 points; dropout: -1 point. The error bar indicates the SD. Differences in response scores were assessed by using one-way analysis of variance (ANOVA) with Tukey's post-hoc test.

*$P < 0.05$; **$P < 0.01$.

Evaluation of adverse drug reactions to Shakuyaku-kanzo-to

No patients experienced adverse drug reactions except one patient who had dizziness: an 80-year-old man with a history of cerebral infarction experienced dizziness during treatment. The administration of Shakuyaku-kanzo-to was stopped and the symptom disappeared. Furthermore, regular blood tests showed no abnormal findings in any patient. One patient reported that postherpetic neuralgia (PHN), in addition to the painful muscle cramps, was alleviated.

DISCUSSION

Painful muscle cramps often occur in the gastrocnemius muscle. Its pathogenic mechanism was suggested to be a disorder of secondary neurons, but details of the mechanism are not clear at present (1). Underlying diseases that cause painful muscle cramps include diabetes, liver cirrhosis, chronic renal failure (hemodialysis), electrolyte abnormalities, and spondylosis deformans (lumbar spondylosis) (11). In our pain clinic, many outpatients suffer from low back and leg pain associated with lumbar spinal stenosis. They are generally treated by a nerve block that is mainly an epidural block. However, careful evaluation has shown that in many cases these symptoms occur together with painful muscle cramps. Treatments for painful muscle cramps include physical therapy such as stretching exercises, thermotherapy, traction therapy, and use of medications such as anticonvulsants, muscle relaxants, and vitamin B12 (2, 3, 10). Eperisone hydrochloride is one of the widely used muscle relaxants for muscle cramps. And Shakuyaku-kanzo-to is a Kampo medicine that is effective for crampy pain in the gastrointestinal smooth muscle and in skeletal muscle. It also reportedly has high therapeutic effectiveness for muscle cramps in patients undergoing dialysis, patients with diabetes or liver cirrhosis, and patients with dysmenorrhea (6, 7, 16).

Shakuyaku-kanzo-to consists of a combination of *P. lactiflora* and *Glycyrrhiza*. Paeoniflorin, which is a major active ingredient of *P. lactiflora*, has sedative, antispastic, and analgesic effects and causes peripheral artery vasodilation. Glycyrrhizin, which is a major active ingredient of *Glycyrrhiza*, has sedative, analgesic, and anti-inflammatory effects (4, 15). In the drug information for Shakuyaku-kanzo-to extract, the prescribed dose is generally 7.5 g/day (given in divided doses twice or three times daily) for sudden muscle cramps in adult patients (13). In this study, we first prescribed 7.5 g/day of Shakuyaku-kanzo-to extract for 16 patients with lumbar spinal stenosis accompanied by painful muscle cramps. After 2 weeks, the frequency of painful muscle cramps decreased by more than 50% in about 87% of the 16 patients. The period required for the maximum therapeutic effect was less than 3 days in most patients, as well as in previous reports (7), whereas some patients required 1-2 weeks to achieve the maximum therapeutic effect. The reason for this longer time requirement may be a change in the intestinal bacterial flora caused by several days of administration of Shakuyaku-kanzo-to, which may have affected the metabolism of paeoniflorin (12).

Adverse reactions to Shakuyaku-kanzo-to can include hypokalemia and pseudoaldosteronism, which should be of special concern. Such adverse reactions are caused by glycyrrhizin, which is found in *Glycyrrhiza*, a component of Shakuyaku-kanzo-to. A glycyrrhizin metabolite, glycyrrhizic acid, inhibits the activity of 11β-hydroxysteroid dehydrogenase, which in turn inhibits the transformation of cortisol to cortisone and thereby results in a high blood level of cortisol (8). Shakuyaku-kanzo-to has reportedly caused serious arrhythmia, cardiac failure, and hypokalemic rhabdomyolysis (9), and it should thus be administered with great care. Yoshida et al. compared the therapeutic efficacy of eperisone hydrochloride and Shakuyaku-kanzo-to for painful muscle cramps (16). They reported that the effect of Shakuyaku-kanzo-to was superior to that of eperisone hydrochloride; however, once the administration of the medicines stopped, the therapeutic effect of Shakuyaku-kanzo-to was more likely to decrease compared with that of eperisone hydrochloride. In addition, long-term administration of Shakuyaku-kanzo-to may be necessary, because painful muscle cramps accompanied by an underlying disease are considered to be intractable unless the primary disease has been cured. However, long-term routine administration of Shakuyaku-kanzo-to may cause adverse drug reactions, as previously described. We believe that in clinical practice it is important to keep the Shakuyaku-kanzo-to dosage as low as possible, in addition to following the standard cautions such as do not administer to patients with hypokalemia or muscle diseases, avoid using in combination with other drugs containing *Glycyrrhiza*, and conduct blood tests.

In this study, we found that one patient showed pain reduction of his post herpetic neuralgia associated pain with Shakuyaku-kanzo-to. PHN causes intractable pain, and the Kampo medicines Oren-gedoku-to (Huang-Lian-Jie-Du-Tang) and Sairei-to (Chai-Ling-Tang) were reportedly effective in the treatment of PHN (5). The effect of Shakuyaku-kanzo-to on PHN has not yet been reported. Additional investigations are needed for an evaluation of the therapeutic effects of Shakuyaku-kanzo-to on PHN.

The limitation of this study is that as we conducted ANOVA to evaluate the each group, there may happen alpha-error, so we should include more number of participants to avoid this error.

In this study, we analyzed the effectiveness of Shakuyaku-kanzo-to for painful muscle cramps associated with lumbar spinal stenosis. The frequency of painful muscle cramps was reduced in 14 of 16 patients, whereas eperisone hydrochloride achieved the same reduction level in 4 of 14 patients. The onset of the maximum therapeutic effect was less than 3 days from the start of administration in 11 of 16 patients. No serious adverse reactions were observed, except for dizziness that was experienced by one patient. The dosage of 2.5 g of Shakuyaku-kanzo-to as needed had a therapeutic effect that was equal to the regular use of 7.5 g/day for painful muscle cramps. In conclusion, our data show that Shakuyaku-kanzo-to is effective for painful muscle cramps associated with lumbar spinal stenosis.

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REFERENCES

1. **Adams, D.R., and Victor, M.** 1981. Disorders of muscle characterized by cramp, spasm, pain, and localized masses. In: Adams, D.R., and Victor, M. (eds.), Principles of Neurology. New York: McGraw-Hill, 940-979.
2. **Bertolasi, L., De Grandis, D., Bongiovanni, L.G., Zanette, G.P., and Gasperini, M.** 2012. The influence of muscular lengthening on cramps. Ann Neurol 1993;**33:**176-180.
3. **Blyton, F., Chuter, V., Walter, K.E., and Burns, J.** Non-drug therapies for lower limb muscle cramps. Cochrane Database Syst Rev **1:**CD008496.
4. **Davis, E.A., and Morris, D.J.** 1991. Medicinal uses of licorice through the millennia: the good and plenty of it. Moll Cell Endocrinol **78:**1-6.
5. **Hijikata, Y.** 2006. Analgesic treatment with Kampo prescription. Expert Rev Neurother **6:**795-802.
6. **Hinoshita, F., Ogura, Y., Suzuki, Y., Hara, S., Yamada, A., Tanaka, N., Yamashita, A., and Marumo, F.** 2003. Effect of orally administered shao-yao-gan-cao-tang (Shakuyaku-kanzo-to) on muscle cramps in maintenance hemodialysis patients: a preliminary study. Am J Chin Med **31:**445-453.
7. **Hyodo, T., Taira, T., Takemura, T., Yamamoto, S., Tsuchida, M., Yoshida, K., Uchida, T., Sakai, T., Hidai, H., and Baba, S.** 2006. Immediate effect of Shakuyaku-kanzo-to on muscle cramp in hemodialysis patients. Nephron Clin Pract **104:**c28-32.
8. **Ihaka, R., and Gentleman, R.** 1996. R: a language for data analysis and graphics. J Comput Graph Stat **5**:299-314.
9. **Kageyama, Y., Suzuki, H., and Saruta, T.** 1992. Glycyrrhizin induces mineralocorticoid activity through alterations in cortisol metabolism in the human kidney. J Endocrinol **135:**147-152.
10. **Kinoshita, H., Okabayashi, M., Kaneko, M., Yasuda, M., Abe, K., Machida, A., Ohkubo, T., Kamata, T., and Yakushiji, F.** 2009. Shakuyaku-kanzo-to induces pseudoaldosteronism characterized by hypokalemia, rhabdomyolysis, metabolic alkalosis with respiratory compensation, and increased urinary cortisol levels. J Altern Complement Med **15:**439-443.
11. **Mauskop, A.** 2010. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology **75:**1397; author reply 1398-1399.
12. **Parisi, L., Pierelli, F., Amabile, G., Valente, G., Calandriello, E., Fattapposta, F., Rossi, P., and Serrao, M**. 2003. Muscular cramps: proposals for a new classification. Acta Neurol Scand **107:**176-186.
13. **Tashiro, S.** 1996. Pharmacological study of application of Shao-Yao-Gan-Cao-Tang for pain with muscle cramps. 41th Annual Meeting of the Japan Society for the Study of Chronic Pain 67.
14. **Tsumura Co. Ltd.** Product Catalogue. Tsumura Kampo Medicine Extract Granules for Ethical Use.
15. **Walker, B.R., and Edwards, C.R.** 1994. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. Endocrinol Metab Clin North Am **23:**359-377.
16. **Yamahara, J., Yamada, T., Kimura, H., Sawada, T., and Fujimura, H.** 1982. Biologically active principles of crude drugs. II. Anti-allergic principles in "Shoseiryu-To" anti-inflammatory properties of paeoniflorin and its derivatives. J Pharmacobiodyn **5:**921-929.
17. **Yoshida, M., Kitaoka, H., and Masui, Y.** 1995. Effect of Shao-Yao-Gan-Cao-Tang for painful muscle cramps in diabetes patients. Therapeutic Neurology **6:**529-534.