A novel anti-dysmenorrhea therapy with cyclic administration of two Japanese herbal medicines

T. Tanaka

Department of Obstetrics & Gynecology, Wakayama Medical University, Wakayama (Japan)

Summary

Purpose and Methods: Using two Japanese herbal medicines, Shakuyaku-kanzo-to (SK) and Toki-shakuyaku-san (TS), we have evaluated a novel strong antidysmenorrhea therapy, SK/TS cyclic therapy, in which the herbs are administered alternately within the menstrual cycle.

Results: All of the 17 dysmenorrhea patients including recurrent endometriotic and adenomyotic patients after treatment with gonadotropin-releasing hormone agonists or danazol, obtained complete relief within three months when treated with the SK/TS cyclic therapy. Nine of 12 patients treated with the SK/TS cyclic therapy ovulated as determined by biphasic changes in basal body temperature patterns. All the three secondary ammenorrhea patients with moderate levels of serum estradiol, but not the three secondary amenorrhea patients with little serum estradiol, ovulated during the SK/TS cyclic therapy. One of the treated patients, who had a history of 10 repetitive spontaneous abortions, carried the 11th pregnancy to term resulting in a normal newborn.

Conclusion: The SK/TS cyclic therapy can be a conservative antidysmenorrhea therapy for endometriotic and adenomyotic patients who desire pregnancy.

Key words: Shakuyaku-kanzo-to, Toki-shakuyaku-san, Endometriosis, Adenomyosis, Dysmenorrhea.

Introduction

Gonadotropin releasing hormone agonists (GnRHa) are presently the most common therapeutic drugs for severe dysmenorrhea patients complicated with endometriosis and/or adenomyosis. However, GnRHa therapy cannot be applied over a long period because of adverse effects such as severe menopausal symptoms and rapid decrease in bone mineral density. Dysmenorrhea easily relapses after cessation of GnRHa therapy, especially in younger patients, and patients during GnRHa therapy cannot get pregnant. Cyclic administrations of contraceptive hormones may have some effect on prevention of the recurrence of endometriosis or adenomyosis after GnRHa therapy, but are not applicable to patients who want to get pregnant because of their inhibitory effects on ovulation. In Japan, Keishi-bukuryo-gan, an antiendometriotic Japanese herbal medicine, is often administered to patients to treat mild endometriosis and adenomyosis, or to prevent the relapse of endometriosis/adenomyosis after GnRHa therapy [1]. However, it is sometimes difficult to suppress severe endometriosis or adenomyosis by Keishi-bukuryo-gan therapy alone. The only method to suppress severe dysmenorrhea while maintaining stable monthly ovulation for pregnancy, therefore, was a combination therapy with both nonsteroidal anti-inflammatory drugs (NSAID) during menstruation and ovulation-inducing medicines. Since this combination is an anti-symptomatic and not an anti-causative therapy for endometriosis/adenomyosis patients, it cannot be used over long periods. We have been looking for a novel Japanese herbal medicine therapy by which severe dysmenorrhea complicated with endometriosis and adenomyosis can be completely suppressed and in which ovulation is not inhibited. Even in the long history of oriental medicine, there is no report of a standard oriental medicine that needs continuous daily intakes of definite medicines thereby suppressing severe dysmenorrhea but without any inhibition of ovulation.

Cyclic administrations of contraceptive hormones can suppress dysmenorrhea and ovulation simultaneously. Cyclic administrations during a perimenstrual period of Shakuyaku-kanzo-to, which is the most popular Japanese herbal medicine against dysmenorrhea in Japan, may sometimes cure patients with functional dysmenorrhea almost completely. These facts suggest that cyclic administration of medicines may be one of the most important factors in treating severe dysmenorrhea. Therefore, we tried cyclic administrations of various combinations of Japanese herbal medicines for severe dysmenorrhea patients with endometriosis or adenomyosis, and finally settled on a strong anti-dysmenorrhea combination therapy using two Japanese herbal medicines, our "SK/TS cyclic therapy". The SK/TS cyclic therapy is an alternate administration of two Japanese herbal medicines, Shakuyaku-kanzo-to (SK) and Toki-shakuyaku-san (TS), adjusting each of the medicines to menstrual cycles. The results of a preliminary study on SK/TS cyclic therapy are presented and the mechanisms of its antidysmenorrhea and ovulation effects are also discussed.

Revised manuscript accepted for publication January 22, 2003

Materials and Methods

SK/TS cyclic therapy: Menstrual cycle-dependent alternate administrations of Shakuyaku-kanzo-to and Toki-shakuyaku-san (Figure 1)

Japanese herbal medicines are mixtures of several herbs that are prodrugs. Both the SK and TS used in this preliminary study were products supplied by a pharmaceutical company for oriental herbal medicines, Tsumura & Co. (Tokyo, Japan). All products (7.5 g per day) were taken orally three times per day between meals as described in Figure 1. Administration of SK (7.5 g per day) was started about seven days before menstruation and stopped at the end of menstruation. And then TS (7.5 g per day) was administered until about seven days before menstruation. The therapeutic effectiveness of the herbal medicines on dysmenorrhea was determined based on patient ratings. Patients reported complete response (CR), i. e., elimination of dysmenorrhea; partial response (PR), i. e., partial relief from dysmenorrhea; or no effect. Ovulation was diagnosed according to stable higher basal body temperature patterns for more than seven days.

Shakuyaku-kanzo-to (SK)

The herbal compound Shakuyaku-kanzo-to (SK) is a mixed prodrug of two herbs consisting of glycyrrhiza root and peony root (the root of *Paeonia lactiflora* Pallas or allied plants (*Paeoniaceae*)). It has been traditionally given to the patients in East Asia to relieve their colic, lumbago, ischialgia, cramps, tension of cervical muscles, and distortion. According to the manufacturer's drug information book, 7.5 g of TSUMURA Shakuyaku-kanzo-to extract granules for ethical use contains 5.0 g of dried extracts obtained from mixed raw herbs in a 1:1 ratio of glycyrrhiza root and of peony root.

Toki-shakuyaku-san (TS)

The herbal compound Toki-shakuyaku-san (TS) is a mixed prodrug of six herbs consisting of peony root, Atractylodes Lancea rhizome, Alisma rhizome, hoelen (the sclerotium of *Poria cocos* Wolf (*Polyporaceae*), usually from which the outer layer has been mostly removed), Cnidium rhizome, and Japanese Angelica root. It has been traditionally given to patients in East Asia to relieve their menopausal symptoms, cold limbs, infertility, dysmenorrhea, shoulder stiffness, symptoms during pregnancy, etc. According to the manufacturer's drug information book, 7.5 g of TSUMURA Toki-shakuyaku-san Extract Granules for Ethical Use contains 4.0 g of dried extract obtained from mixed raw herbs in the ratio: 4.0 g of peony root, 4.0 g of Atractylodes Lancea rhizome, 4.0 g of Alisma rhizome, 4.0 g of hoelen, 3.0 g of Cnidium rhizome, 3.0 g of Japanese Angelica root.

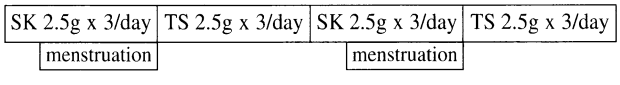

Figure 1. — SK/TS cyclic therapy: Menstrual cycle-dependent alternate administration of Shakuyaku-kanzo-to and Toki-shakuyaku-san.
Shakuyaku-kanzo-to (SK) and Toki-shakuyaku-san (TS) were taken orally 3 times per day (7.5 g per day) between meals. Administration of SK (7.5 g per day) was started about 7 days before menstruation and stopped at the end of menstruation. And then TS (7.5 g per day) was administered until about 7 days before menstruation.

Patients (Table 1)

The 25 patients treated with SK/TS cyclic therapy from September 1999 to September 2002 in the Gynecologic Outpatient Clinic for Endocrinology/Oriental Medicine of the University Hospital are summarized in Table 1. The main causative diseases of the 25 patients include nine endometriosis, two adenomyosis, six functional dysmenorrhea, two habitual abortion, and six secondary ammenorrhea. Diagnoses of endometriosis and adenomyosis were made according to laparoscopic findings and magnetic resonance imagings. The SK/TS cyclic therapy was performed from two to 20 months.

Table 1. — *Patients treated with SK/TS cyclic therapy.*

Patients	No. of cases
Endometriosis	9
Adenomyosis	2
Functional dysmenorrhea	6
Habitual aborter	2
Secondary amenorrhea (peak serum estradiol > 25 pg/ml)	3
Secondary amenorrhea (peak serum estradiol < 25 pg/ml)	3
Total	25

Results

No adverse effects were found in the patients treated with SK/TS cyclic therapy during this study.

Effects of SK/TS cyclic therapy on dysmenorrhea (Table 2)

Effects of SK/TS cyclic therapy on 17 patients complaining of dysmenorrhea are summarized in Table 2. Antidysmenorrhea effects were found after one cycle of SK/TS cyclic therapy, and dysmenorrhea completely disappeared in all patients within three cycles of the therapy. During the SK/TS cyclic therapy, no apparent reduction of menorrhagia was found in any of the patients. Out of these 17 dysmenorrhea patients, three had relapsed

Table 2. — *Effects of SK/TS cyclic therapy on dysmenorrhea.*

Patients No.	Causes of dysmenorrhea	Age	Cycles	Result
1	Endometriosis. Recurrence after the GnRHa therapy	32	10	CR
2	Endometriosis. Recurrence after the GnRHa therapy	26	14	CR
3	Adenomyosis. Recurrence after the GnRHa therapy	46	12	CR
4	Endometriosis. Recurrence after the danazol therapy	36	8	CR
5	Endometriosis. Recurrence after the danazol therapy	20	11	CR
6	Endometriosis	38	4	CR
7	Endometriosis	39	7	CR
8	Endometriosis	21	10	CR
9	Endometriosis	49	4	CR
10	Endometriosis	27	3	CR
11	Adenomyosis	23	2	CR
12	Functional dysmenorrhea	24	4	CR
13	Functional dysmenorrhea	28	4	CR
14	Functional dysmenorrhea	23	2	CR
15	Functional dysmenorrhea	28	4	CR
16	Functional dysmenorrhea	19	20	CR
17	Functional dysmenorrhea	42	4	CR

endometriosis/adenomyosis after GnRHa therapy, including two cases with two previous cycles of GnRHa therapy. Two of the 17 patients were recurrent cases after danazol therapy.

Effects of SK/TS cyclic therapy on ovulation (Table 3)

Table 3 shows 12 cases that had information regarding their ovulation. Twelve patients recorded their basal body temperatures and nine of the 12 ovulated during the SK/TS cyclic therapy. Three ammenorrhea patients with low serum estradiol levels (peak serum estradiol < 25 pg/ml) did not have any ovulation during the SK/TS cyclic therapy. However, ovulation was induced in three secondary ammenorrhea patients with moderate levels of serum estradiol (peak serum estradiol > 25 pg/ml) during the SK/TS cyclic therapy. Patient 18 with habitual abortions, who had had ten repetitive spontaneous abortions before, had an 11th pregnancy during the SK/TS cyclic therapy and delivered a normal newborn.

Table 3. — *Effects of SK/TS cyclic therapy on ovulation.*

Patients No.	Causes of dysmenorrhea, anovulation and infertility	Age	Cycles	Ovulation
4	Endometriosis. Recurrence after the danazol therapy	36	8	Yes
6	Endometriosis	38	4	Yes
11	Adenomyosis	23	2	Yes
15	Functional dysmenorrhea	28	4	Yes
18	Infertility (habitual abortion)	41	2	Yes (achieved pregnancy)
19	Infertility (habitual abortion)	33	4	Yes
20	Secondary amenorrhea (with moderate estradiol, non-PCOS)	22	2	Yes
21	Secondary amenorrhea (with moderate estradiol, non-PCOS)	26	8	Yes
22	Secondary amenorrhea (with moderate estradiol, PCOS)	25	8	Yes
23	Secondary amenorrhea (with little estradiol)	21	2	No
24	Secondary amenorrhea (with little estradiol)	26	2	No
25	Secondary amenorrhea (with little estradiol)	26	4	No

PCOS: polycystic ovary syndrome.

Effects of SK/TS cyclic therapy on serum CA125 levels (Figures 2)

Serum CA125 levels during the SK/TS cyclic therapy were examined on four patients with endometriosis or adenomyosis. As shown in Figure 2, elevated serum CA125 levels decreased during the SK/TS cyclic therapy.

Discussion

All the 17 patients with severe dysmenorrhea had complete relief with SK/TS cyclic therapy within three months. Five of the 17 patients were endometriosis or adenomyosis patients who relapsed after GnRHa therapy or Danazol therapy. These results indicate that SK/TS cyclic therapy is effective on severe dysmenorrhea complicated with endometriosis or adenomyosis. Patients complaining of hypermenorrhea in the study did not have any significant relief for their hypermenorrhea. However, endometriotic or adenomyotic patients whose serum CA125 levels were examined during the SK/TS cyclic therapy showed gradual decreases in CA125 levels during the therapy (Figure 2). This suggests that SK/TS cyclic therapy may suppress advancement of endometriosis/adenomyosis lesions.

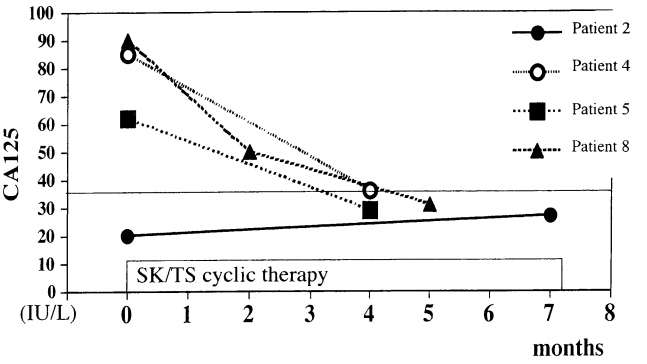

Figure 2. — Effects of SK/TS cyclic therapy on serum CA125 levels in endometriotic and adenomyotic patients.

Some of the dysmenorrhea patients treated with SK/TS cyclic therapy complained of increased lower abdominal pain during ovulation instead of a decrease in dysmenorrhea. The 12 cases who recorded their basal body temperatures showed whether ovulation can be inhibited by SK/TS cyclic therapy or not. Two habitual aborters with regular ovulatory cycles showed no inhibitory effects on ovulation during the SK/TS cyclic therapy. Patient 18, for example, a 41-year-old habitual aborter with a history of ten repeated spontaneous abortions, got pregnant during the SK/TS cyclic therapy and delivered a healthy newborn. Ovulations were found in two endometriotic patients (Patients 4 and 6), one adenomyotic patient (Patient 11) and Patient 15 with functional dysmenorrhea according to their basal body temperature records. From these results, it can be said that SK/TS cyclic therapy does not inhibit ovulation. SK/TS cyclic therapy was also tried on six patients with secondary amenorrhea. The SK/TS cyclic therapy caused ovulations in three secondary amenorrhea patients with moderate levels of serum estradiol. However, three with low endogenous estradiol levels did not have any ovulation during the therapy. Although it is unclear if the SK/TS cyclic therapy may have induced ovulation, SK/TS cyclic therapy may be one of the best therapies for patients with severe dysmenorrhea who desire pregnancy.

It is not clearly understood why SK/TS cyclic therapy inhibits severe dysmenorrhea without inhibition of ovulation. Both SK and TS are reported to inhibit production of prostaglandins that can induce dysmenorrhea [2]. SK is composed of 50% w/w of Shakuyaku and 50%w/w of Kanzo. Shakuyaku is also included in TS. Paeoniflorin, a possible major effective pharmacological component in

Shakuyaku, and glycyrrhetic acid and glycyrrhizin, possible major effective components in Kanzo, are reported to relax constriction of smooth and skeletal muscles [3-7]. Today SK is often used for cancer patients complaining of arthralgia caused by paclitaxel, an anticancer drug [8]. In SK/TS cyclic therapy, therefore, SK that is administered to patients around the perimenstrual period, may be a major antidysmenorrhea medicine. Since SK suppresses adenomyosis lesions in adenomyosis model mice with pituitary implants in the uterus [9], SK in SK/TS cyclic therapy might inhibit cell proliferation of endometriosis/adenomyosis lesions in patients as shown in Figure 2.

Both SK and TS are reported to have specific endocrine functions. SK inhibits drug-induced hyperprolactinemia [10, 11] and amenorrhea [12]. SK is also reported to suppress production of testosterone and induce ovulation in patients with polycystic ovary syndrome [13-15]. TS has various endocrine effects on pituitary-ovary functions [16-20] and it is one of the most popular herbal medicines for anovulatory patients in Japan [21-23]. These facts indicate that cyclic administration of these two Japanese herbal medicines, which have both antidysmenorrhea and ovulatory effects, may induce a stable endocrine state to inhibit dysmenorrhea and possibly stimulate ovulation. However ovulatory effects by SK/TS cyclic therapy may need certain levels of stimulated granulosa cells that produce estradiol, because ovulation could not be induced in the three secondary ammenorrhea patients with low serum estradiol levels (estradiol < 25 pg/ml). As cyclic intake of oral contraceptive hormones usually suppresses ovulation, hypermenorrhea and dysmenorrhea, the cyclic alternate administration of these two Japanese herbal medicines, which have been reported to have endocrine functions, is welcome as it introduces a stable endocrine condition in patients to suppress severe dysmenorrhea without any suppression of ovulation. SK/TS cyclic therapy is applicable, as a novel antidysmenorrhea therapy, for patients with endometriosis or adenomyosis who desire pregnancy.

Acknowledgments

This work was supported in part by Grants-in-Aids for scientific research from the Ministry of Education, Science, Sports and Culture of Japan, and a grant-in-aid from the Japan Research Fund of Institute of Kampo Medicine.

References

[1] Tanaka T., Umesaki N., Mizuno K., Fujino Y., Ogita S.: "Antiendometrial IgM autoantibodies in endometriotic patients: a preliminary study". *Clin. Exp. Obst. Gyn.,* 2000, *27,* 133.

[2] Imai A., Horibe S., Fuseya S., Iida K., Takagi H., Tamaya T.: "Possible evidence that the herbal medicine shakuyaku-kanzo-to decreases prostaglandin levels through suppressing arachidonate turnover in endometrium". *J. Med.,* 1995, *26,* 163.

[3] Maeda T., Shinozuka K., Baba K., Hayashi M., Hayashi E.: "Effect of shakuyaku-kanzoh-toh, a prescription composed of shakuyaku (Paeoniae Radix) and kanzoh (Glycyrrhizae Radix) on guinea pig ileum". *J. Pharmacobiodyn.,* 1983, *6,* 153.

[4] Kimura M., Kimura I., Muroi M., Nakamura T., Shibata S.: "Depolarizing effects of glycyrrhizin-derivatives relating to the blend effects with paeoniflorin in mouse diaphragm muscle". *Jpn. J. Pharmacol.,* 1986, *41,* 263.

[5] Dezaki K., Kimura I., Miyahara K., Kimura M.: "Complementary effects of paeniflorin and glycyrrhizin on intracellular Ca2+ mobilization in the nerve-stimulated skeletal muscle of mice". *Jpn. J. Pharmacol.,* 1995, *69,* 281.

[6] Bando M., Shibahara N., Shimada Y. *et al.*: "Pharmacokinetic study of paeoniflorin, paeonimetabolin-I and glycyrrhetic acid in humans after oral administration of paeony root, glycyrrhiza and Shakuyaku-kanzo-to". *J. Trad. Med.,* 2000, *17,* 26.

[7] Tanaka T., Umesaki N., Ogita S.: "Thawing of frozen shoulder in menopausal women treated with a Japanese herbal medicine, Kanzo-to extract: report of two cases". *Clin. Exp. Obst. Gyn.,* 2000, *27,* 14.

[8] Yamamoto K., Hoshiai H., Noda K.: "Effects of shakuyaku-kanzo-to on muscle paon from combination chemotherapy with paclitaxel and carboplatin". *Gynecol. Oncol.,* 2001, *81,* 333.

[9] Mori T., Sakamoto S., Matsuda M. *et al.*: " Suppression of spontaneous development of uterine adenomyosis and mammary hyperplastic alveolar nodules by Chinese herbal medicines in mice". *Am. J. Chin. Med.,* 1993, *21,* 263.

[10] Yamada K., Kanba S., Murata T., et al.: " Effectiveness of herbal medicine (shaukuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia: a preliminary report". *Psychiatry Clin. Neurosci.,* 1996, *50,* 341.

[11] Yamada K., Kanba S., Yagi G., Asai M.: "Effectiveness of herbal medicine (shaukuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia". *J. Clin. Psycopharmacol.,* 1997, *17,* 234.

[12] Yamada K., Kanba S., Yagi G., Asai M.: "Herbal medicine (Shakuyaku-kanzo-to) in the treatment of risperidone-induced amenorrhea". *J. Clin. Psycopharmacol.,* 1999, *19,* 380.

[13] Sakamoto K., Wakabayashi K.: "Inhibitory effect of glycyrrethinic acid on testosterone production in rat gonads". *Endocrinol. Jpn.,* 1998, *35,* 333.

[14] Takeuchi T., Nishii O., Okamura T., Yaginuma T.: "Effect of paeoniflorin, glycyrrhizin and glycyrrhetic acid on ovarian production". *Am. J. Chin. Med.,* 1991, *19,* 73.

[15] Takahashi K, Kitao M.: "Effect of TJ-68 (shakuyaku-kanzo-to) on polycystic ovarian disease". *Int. J. Fertil. Menopausal. Stud.,* 1994, *39,* 69.

[16] Usuki S.: "Effects of hachimijiogan, tokishakuyakusan and keishibukuryogan on estrogen and progesterone secretions by rat preovulatory follicles". *Am. J. Chin. Med.,* 1986, *14,* 161.

[17] Usuki S.: "Effects of tokishakuyakusan and keishibukuryogan on steroidgenesis by rat preovulatory follicles incubated in vivo". *Am. J. Chin. Med.,* 1990, *18,* 149.

[18] Usuki S.: "Effects of hachimijiougan, tokishakuyakusan, keishibukuryogan, ninjinto and unkeito on estrogen and progesterone secretion in preovulatory follicles incubated in vitro". *Am. J. Chin. Med.,* 1991, *19,* 65.

[19] Usuki S, Usuki Y, Tanaka J, Kawakura Y. Effects of tokishakuyakusan, keishibukuryogan, shakuyakukanzoto and unkeito on ovarian endithelin, renin and angiotensin II in pregnant mare's serum gonadotropin-treated immature rats. *Am. J. Chin. Med.,* 1992, *20,* 175.

[20] Usuki S., Tanaka J., Kawakura Y., Usuki Y.: "A proposal of ovarian ERAANPS (endothelin-renin-angiotensin-atrial natriuretic peptide system) and effects of tokishakuyakusan, keishibukuryogan, shakuyakukanzoto and unkeito on the ERAANPS". *Am. J. Chin. Med.,* 1992, *20,* 65.

[21] Koyama T., Ohara M., Ishimura M., Saito M.: "Effect of Japanese kampo medicine on hypothalamic-pituitary-ovarian function in women with ovarian insufficiency". *Am. J. Chin. Med.,* 1988, *16,* 47.

[22] Koyama T., Hagino N., Cothron A. W., Saito M.: "Effect of tikishakuyaku-san on ovulation induced by human menopausal gonadotropin in rats". *Am. J. Chin. Med.,* 1988, *16,* 169.

[23] Koyama T., Hagino N., Cothron A.W., Saito M.: "Neuroendocrine effects of toki-shakuyaku-san on ovulation in rats". *Am. J. Chin. Med.,* 1989, *17,* 29.

Address reprint requests to:
T. TANAKA, M.D., Ph.D.
Department of Obstetrics & Gynecology
Wakayama Medical University
811-1 Kimi-idera,
Wakayma 641-0012 (Japan)