

# Effects of herbal medicines on menopausal symptoms induced by gonadotropin-releasing hormone agonist therapy

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## Summary

The therapeutic effects of certain Japanese herbal medicines on menopausal symptoms induced by gonadotropin-releasing hormone agonist therapy were examined in Japanese women with endometriosis, adenomyosis, or leiomyoma. Menopausal symptoms occurred in 17 of the 22 patients. Toki-shakuyaku-san, Shakuyaku-kanzo-to, Keishi-bukuryo-gan, Kami-shoyo-san, Tokaku-joki-to, or Keishi-to was administered to 13 of the 17 patients with menopausal symptoms, and efficacy was observed in all 13. Eleven patients with hot flashes were treated with Toki-shakuyaku-san, and all 11 patients experienced some relief; four experienced total relief. Three patients complaining of severe shoulder stiffness were treated with Shakuyaku-kanzo-to and were completely relieved of symptoms. There was no significant change in serum estradiol levels after treatment with the Japanese herbal medicines. Our results indicate that Japanese herbal medicines can be recommended for menopausal symptoms induced by gonadotropin-releasing hormone agonists without a negative effect on serum estradiol levels.

**Key words:** Herbal medicine; Menopausal symptoms; GnRHa; Toki-shakuyaku-san.

## Introduction

Administration of gonadotropin-releasing hormone agonist (GnRHa) induces down regulation of GnRH receptor expression in anterior pituitary cells and results in strong suppression of gonadotropin release from pituitary cells as well as ovarian estradiol production. Thus, GnRHa is applied clinically for estrogen-dependent diseases such as endometriosis, adenomyosis, and leiomyoma to induce lesion atrophy. The low estradiol condition can occur within three months after the start of GnRHa therapy, and serum estradiol levels fall to less than 10 ng/ml. This rapid fall in serum estradiol levels frequently induces menopausal symptoms in GnRHa-treated patients [1, 2].

Hormone replacement therapy is the treatment of choice for patients with menopausal symptoms, and herbal medicine therapy is the second choice in Japan, Korea, and China. Herbal medicines were imported to Japan from Korea and China several centuries ago. These herbal medicines were improved on over time, and thus the Japanese have established their own herbal medicine system. Herbal medicines are used to treat various symptoms in perimenopausal patients in whom hormone replacement therapy has no effect. Spontaneous menopausal symptoms are not always associated with low estrogen conditions, but menopausal symptoms observed in GnRHa-treated patients are always accompanied by low estrogen levels [3]. Thus, the mechanism by which menopausal symptoms are induced by GnRHa can be very different from that of spontaneous menopausal symptoms. Although many researchers have reported the effectiveness of herbal medicines on spontaneous menopausal symptoms, there are few reports showing preventative

and therapeutic effects on GnRHa-induced symptoms. In this study, we examined the therapeutic effects of Japanese herbal medicines on GnRHa-induced menopausal symptoms.

## Patients

We studied 22 Japanese women who had been given leuprolide acetate (Takeda Co., Osaka, Japan) subcutaneously more than five times between January 1997 and December 1999 at Osaka City University Hospital. The major indications for GnRHa therapy in these 22 patients were endometriosis (n=8), adenomyosis (n=5), and leiomyoma (n=9), as shown in Table 1. Endometriosis had been diagnosed according to laparoscopic or laparotomic findings, and adenomyosis or leiomyoma had been diagnosed based on magnetic resonance imaging findings. The GnRHa treatment began with an injection of 3.75 mg of leuprolide acetate every four weeks; leuprolide acetate was administered at 1.88 mg every month after the patient showed amenorrhea and a low serum estradiol level (under 20 ng/ml). The leuprolide acetate was injected subcutaneously into the abdominal wall by the author.

Patient outcomes are summarized in Table 1. Benefits from GnRHa therapy were observed in 20 of the 22 patients; two patients (patients 7 and 17) showed no effect. There was no difference in the efficacy of GnRHa therapy between patients who received Japanese herbal medicines and those who did not. Seventeen of the 22 GnRHa-treated patients complained of menopausal symptoms. Sixteen of the 17 complained of hot flashes. Shoulder stiffness and headache were also common symptoms. No psychological symptoms were found in the 22 patients.

## Japanese herbal medicines

Six Japanese herbal medicines were used: Toki-shakuyaku-san, Shakuyaku-kanzo-to, Keishi-bukuryo-gan, Kami-shoyo-san, Tokaku-joki-to, and Keishi-to (Table 2). These Japanese

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Table 1. — *Patients, indications, herbal medicines used, and outcomes.*

Patient	Age (yrs)	Indication for GnRHa therapy	Menopausal symptoms	First appearance of the symptoms (weeks after start of GnRHa)	Japanese herbal medicines	Effects on menopausal symptoms
1	49	leiomyoma	hot flashes	12	Toki-shakuyaku-san	CR
2	44	leiomyoma	hot flashes	16	Toki-shakuyaku-san	CR
3	44	leiomyoma	episodic sweating, headache	12	Keishi-bukuryo-gan, Tokaku-joki-to, Toki-shakuyaku-san	PR
4	37	leiomyoma	hot flashes, episodic sweating	10	Toki-shakuyaku-san	PR
5	36	leiomyoma	hot flashes, episodic sweating	13	Toki-shakuyaku-san	PR
6	35	leiomyoma	hot flashes	12	Keishi-bukuryo-gan (eruption), Kami-shoyo-san	PR
7	34	leiomyoma	hot flashes	18	None (refused)	—
8	43	adenomyosis	hot flashes, shoulder stiffness	8	Toki-shakuyaku-san, Shakuyaku-kanzo-to	CR
9	47	adenomyosis	hot flashes, shoulder stiffness	16	Toki-shakuyaku-san, Shakuyaku-kanzo-to	CR
10	33	adenomyosis	hot flashes	13	Toki-shakuyaku-san	PR
11	29	endometriosis	hot flashes	10	Toki-shakuyaku-san	PR
12	48	endometriosis	hot flashes, headache, shoulder stiffness	16	Toki-shakuyaku-san (eruption), Shakuyaku-kanzo-to	PR
13	44	endometriosis	hot flashes	24	Keishi-bukuryo-gan	PR
14	44	endometriosis	hot flashes, hair falling	16	Toki-shakuyaku-san, Keishi-to	PR
15	36	endometriosis	hot flashes	10	None (refused)	—
16	34	endometriosis	hot flashes, headache	16	None (refused)	—
17	30	endometriosis	hot flashes	16	None (refused)	—
18	35	leiomyoma	None	—	None	—
19	52	leiomyoma	None	—	None	—
20	49	adenomyosis	None	—	None	—
21	48	adenomyosis	None	—	None	—
22	25	endometriosis	None	—	None	—

CR = complete response; PR = partial response; — = not treated with herbal medicines.

Table 2. — *Japanese herbal medicines administered for menopausal symptoms associated with GnRHa therapy.*

Japanese herbal medicine	Chinese name	Product name	Dose (p.o. 3 times per day)	Composition*	General indications in Japan (ref. 18)
Toki-shakuyaku-san	当帰芍薬散	TSUMURA Toki-shakuyaku-san Extract Granules for Ethical Use	7.5 g/day (4.0 g of dried extracts)	Peony root 4.0 g, Atractylodes Lancea rhizome 4.0 g, Alisma rhizome 4.0 g, Hoelen 4.0 g, Cnidium rhizome 3.0 g, Japanese Angelica root 3.0 g.	Menopausal symptoms, Cold limbs, Infertility, Dysmenorrhea, Shoulder stiffness, Symptoms during pregnancy, etc. (especially in relatively weak patients).
Shakuyaku-kanzo-to	芍薬甘草湯	TSUMURA Shakuyaku-kanzo-to Extract Granules for Ethical Use	15.0 g/day (5.0 g of dried extracts)	Glycyrrhiza root 6.0 g, Peony root 6.0 g.	Colic, lumbago, ischialgia, cramps, tension of cervical muscles, distortion.
Keishi-bukuryo-gan	桂枝茯苓丸	TSUMURA Keishi-bukuryo-gan Extract Granules for Ethical Use	7.5 g/day (1.75 g of dried extracts)	Cinnamon bark 3.0 g, Peony root 3.0 g, Peach Kernel 3.0 g, Hoelen 3.0 g, Mountain bark 3.0 g	Menopausal symptoms, Dysmenorrhea, Shoulder stiffness, etc. (especially in considerably strong patients).
Kami-shoyo-san	加味逍遙散	TSUMURA Kami-shoyo-san Extract Granules for Ethical Use	7.5 g/day (4.0 g of dried extracts)	Bupleurum root 3.0 g, Peony root 3.0 g, Atractylodes Lancea rhizome 3.0 g, Japanese Angelica root 3.0 g, Hoelen 3.0 g, Gardenia fruit 2.0 g, Mountain bark 2.0 g, Glycyrrhiza root 1.5 g, Ginger rhizome 1.0 g, Mentha herb 1.0 g.	Menopausal symptoms, Dysmenorrhea, Shoulder stiffness, Neuro-psychic disturbances, etc. (especially in relatively weak patients).
Tokaku-joki-to	桃核承気湯	TSUMURA Tokaku-joki-to Extract Granules for Ethical Use	7.5 g/day (3.0 g of dried extracts)	Peach Kernel 5.0 g, Cinnamon bark 4.0 g, Rhubarb rhizome 3.0 g, Glycyrrhiza root 1.5 g, Anhydrous Mirabilitum 0.9 g	Menopausal symptoms, Dysmenorrhea, Shoulder stiffness, etc. (especially in stout women).
Keishi-to	桂枝湯	TSUMURA Keishi-to Extract Granules for Ethical Use	7.5 g/day (3.0 g of dried extracts)	Cinnamon bark 4.0 g, Peony root 4.0 g, Jujube fruit 4.0 g, Glycyrrhiza root 2.0 g, Ginger rhizome 1.5 g.	Common cold (especially in pregnant women), and initial status of other infectious diseases accompanied by fever.

\*7.5 g of each product contains 1.75 g, 2.5 g, 3.0 g, or 4.0 g of dried extracts obtained from mixed raw herbs.

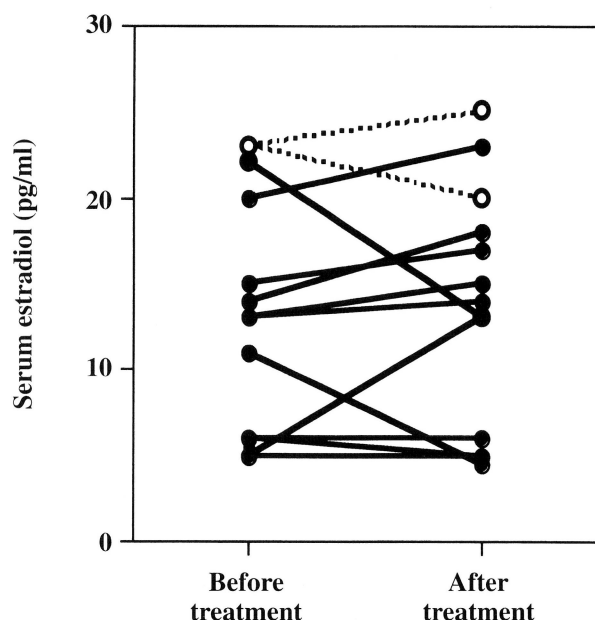


Figure 1. — Effect of Japanese herbal medicines on serum estradiol levels. Solid lines with closed circles show serum estradiol levels in the patients treated with Toki-shakuyaku-san ( $n=11$ ), and dotted lines with open circles show serum estradiol levels in the patients treated with Keishi-bukuryo-gan ( $n=2$ ).

herbal medicines are considered prodrugs and are a mixture of several herbs. All products used were supplied by Tsumura & Co. (Tokyo, Japan). The medicines and their components are summarized in Table 2, which, for the benefit of medical practitioners in East Asia, also shows the names in Chinese. All products (7.5 g or 15.0 g per day) were taken orally three times per day for four weeks. Japanese herbal medicines were administered to 13 patients with menopausal symptoms induced by the GnRHa therapy; four patients refused herbal medicines. Eleven patients with hot flashes were treated with Toki-shakuyaku-san, and patients complaining of severe shoulder stiffness were treated with Shakuyaku-kanzo-to. None of the 22 patients underwent hormone replacement therapy.

The therapeutic effectiveness of the herbal medicines was determined based on patient ratings. Patients reported complete response (CR), i.e., elimination of symptoms; partial response (PR), i.e., partial relief from symptoms; or no effect. Serum estradiol levels were examined by enzyme immunoassay before and after four weeks of treatment with Toki-shakuyaku-san or Keishi-bukuryo-gan in patients treated with GnRHa. The estradiol levels before and after treatment were expressed as mean  $\pm$  SEM and were analyzed with the Student's *t*-test ( $n=13$ ) and ANOVA. Significance was set at  $p<0.05$ .

## Results

Japanese herbal medicines were administered to 13 of the 17 patients with menopausal symptoms, and apparent efficacy was shown in all 13. All 11 patients with hot flashes who were treated with Toki-shakuyaku-san found at least some relief, and four of the 11 reported a complete loss of symptoms. Three patients with severe shoul-

der stiffness were treated with Shakuyaku-kanzo-to, and all were completely cured. The only reported side-effects of the Japanese herbal medicines, were skin eruptions found in Patient 6, who was treated with Keishi-bukuryo-gan, and in Patient 12, who was treated with Toki-shakuyaku-san. The eruptions disappeared completely with cessation of the herbal products. As shown in Figure 1, there were no significant changes in serum estradiol levels in the patients treated with the Japanese herbal medicines for four weeks.

## Discussion

Symptoms associated with spontaneous menopause vary widely and may include chill, heat palpitations, depression, irritability, anxiety, insomnia, buzzing, sleeplessness, dizziness in the ear, general fatigue, night sweating, appetite loss, vertigo, hot flashes, shoulder stiffness, and headache. In the present series, the menopausal symptoms induced by GnRHa therapy were similar among patients. Hot flashes were the most frequent symptoms. This indicates that GnRHa therapy induces similar endocrinological changes in patients. These menopausal symptoms are thought to occur due to an acute low estradiol condition, since symptoms are relieved by estrogen supplement therapy (add-back therapy) [4, 5].

Japanese herbal medicines were administered to 13 patients with menopausal symptoms induced by the GnRHa therapy, and efficacy was demonstrated in all 13. Four of 11 patients treated with Toki-shakuyaku-san showed a complete response. Because there were no significant changes in serum estradiol levels after four weeks of treatment with Toki-shakuyaku-san, the effectiveness of Toki-shakuyaku-san was considered not to be due to estrogen supplemental effects such as with add-back therapy. The pharmacological mechanisms of Japanese herbal medicines remain unclear. As with estrogen, which has been reported to relieve juvenile dementia [11–16], several experiments have shown that Toki-shakuyaku-san has some preventative and therapeutic effects on dementia [12, 13]. We speculate that the steroid-like substances and estrogen-like substances in Japanese herbal medicines might act on menopausal symptoms [14]. Japanese herbal medicines might correct endocrinological imbalances but not low estrogen conditions in patients with menopausal symptoms, since perimenopausal patients with general malaise do not always show low serum estradiol levels [3]. Hot flashes are sometimes experienced by men upon administration of GnRHa. GnRHa results in a fall in testosterone levels [15, 16]. Our results suggest that Japanese herbal medicines could have curative effects in men experiencing GnRHa-induced symptoms.

In the present study, Shakuyaku-kanzo-to was administered to three patients with severe shoulder stiffness, and the stiffness was completely relieved. Shakuyaku-kanzo-to is reported to be effective on frozen shoulder syndrome in menopausal women [17]. The effects of Shakuyaku-

kanzo-to that we observed on shoulder stiffness induced by GnRHa therapy was remarkable.

We have shown beneficial effects of Japanese herbal medicines on menopausal symptoms induced by GnRHa therapy. Because these medicines show pharmacological effects on symptoms without increases in serum estradiol levels, we are encouraged that these Japanese herbal medicines may be very useful alternatives to hormone replacement therapy for GnRHa-induced menopausal symptoms.

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