

Thawing of frozen shoulder in menopausal women treated with a Japanese herbal medicine, Kanzo-to extract: report of two cases

T. Tanaka, N. Umesaki, S. Ogita

Department of Obstetrics and Gynecology, Osaka City University Medical School, Osaka (Japan)

Summary

We report here two patients with frozen shoulder syndrome and severe menopausal symptoms. Short-term administration of Kanzo-to extract thawed the shoulders completely enough for the patients to move their cervical and shoulder joints without any restriction or pain. Their menopausal symptoms were cured simultaneously. Kanzo and Shakuyaku were found to have different effects on shoulder stiffness and disability in shoulder joints.

Key words: Frozen shoulder syndrome; Menopause; Kanzo; Shakuyaku.

Introduction

Perimenopausal women often complain of severe shoulder stiffness associated with cervical/shoulder pain, and some cases are complicated by idiopathic frozen shoulder syndrome (FSS), which is generally characterized as restricted range of motion in the shoulder and cervical joints. Although there have been many reports on the treatment of FSS, no one, to our knowledge, has developed any specific medicinal therapy for FSS to thaw the restricted motion of the shoulder and cervical joints completely within a short time. We recently succeeded in perfect thawing of impaired motion of the shoulder and cervical joints in two women with severe menopausal symptoms by using a Japanese herbal medicine, Kanzo-to extract. We present here the two cases and discuss the effects of Kanzo-to extract on FSS.

Case 1

This patient was a 49-year-old postoperative ovarian cancer patient. Approximately 1 year prior to oophorectomy, she had begun to complain of general malaise with episodic sweating, fatigue, severe shoulder stiffness, sleeplessness, and hot flushes, all characteristic of menopause. Three months after surgery her symptoms worsened, and 6 months after surgery she visited our Menopause Clinic because she could not tolerate these symptoms or sleep without medication. She also complained of an inability to lift her left arm past the horizontal level. She first noticed this frozen shoulder about 1 year before first visiting our clinic. Passive manipulation of her shoulder to raise her left arm caused severe pain in her left shoulder joint. However, she could lift her right arm easily.

In order to relieve her menopausal symptoms, we initially treated her with conjugated estrogen (Premarin™, Asahi-kasei Co.; Nobeoka, Japan, 0.625 mg daily), medroxyprogesterone acetate (Provera™, Pharmacia-Upjohn Japan Co.; Tokyo, Japan; 2.5 mg daily), and a Japanese herbal medicine, Toki-

shakuyaku-san extract (Tsumura Co., Tokyo, Japan; 2.5 g, 3 times a day). Toki-shakuyaku-san is the most popular herbal medicine used in Japan for menopausal symptoms and contains 18.2% w/w Shakuyaku (Peony root) but no Kanzo (Glycyrrhiza root). Three months of the therapy partially alleviated the patient's menopausal symptoms but did not reduce her FSS. Oral administration of 25 mg diclofenac sodium (Voltaren™, Chiba-Geigy Japan, Co., Tokyo, Japan), a prostaglandin synthesis inhibitor, along with sleeping pills and the application of multiple poultices relieved her shoulder stiffness slightly and helped her sleep. Thirty minutes after oral administration of 5 g of Shakuyaku-kanzo-to extract (Japanese herbal medicine combined with 50% w/w Shakuyaku and 50% w/w Kanzo) (Tsumura Co.), the patient felt relaxation of the muscles of her neck and shoulders, and she could sleep comfortably without medication. However, Shakuyaku-kanzo-to did not affect her FSS. Thereafter, 2 g of Kanzo-to extract (Japanese herbal medicine composed of 100% w/w Kanzo) (Kanebo Ltd., Tokyo, Japan) was administered orally once a day. Surprisingly, she could raise her left arm to 30 degrees over the horizontal level on the 5th day after starting on Kanzo-to, to 45 degrees on the 6th day, to 60 degrees on the 7th day, to 65 degrees on the 8th day, and to 70 degrees on the 14th day. She continued to take Kanzo-to extract for 2 months, and by the 50th day she could raise her left arm over her head without any limitation (Fig. 1). Interestingly, her menopausal symptoms were also completely relieved after 2 months of oral intake of Kanzo-to extract. No adverse effects of Kanzo-to extract were observed.

Case 2

This patient was a 50-year-old nurse-in-chief of our university hospital with menopausal symptoms including hot flushes, sleeplessness, severe shoulder stiffness, and episodic sweating. Her neck was so frozen that she could not turn her head bilaterally or look at the ceiling. She could turn her head only to 70 degrees bilaterally or 75 degrees upward. She was first treated with Kami-shoyo-san extract (Tsumura Co., Tokyo, Japan; 2.5 g, 3 times a day) for 2 months, but this herbal medicine only partially relieved her menopausal symptoms. Kami-shoyo-san extract is another of the most popular herbal medicines used in Japan for menopausal symptoms, and it contains 13.3% w/w

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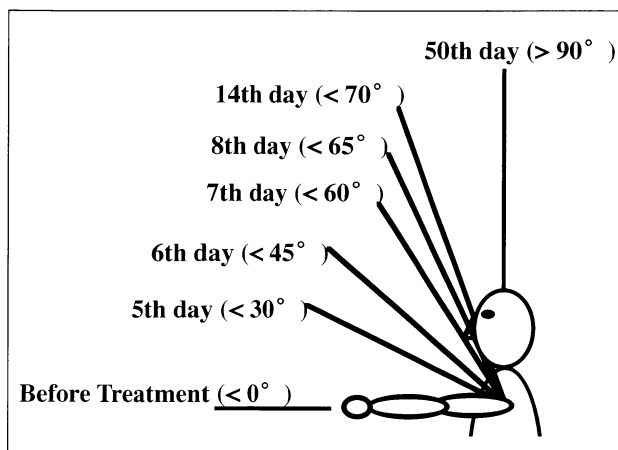


Figure 1. — Effects of Kanzo-to extract (2 g/day) on frozen shoulder in Patient 1.

Shakuyaku and 6.67% w/w Kanzo. We then administered Kanzo-to extract to this patient because our prior patient had been cured dramatically with this herbal medicine. With only 6 oral administrations of Kanzo-to extract (2 g x 6), it became possible for this second patient to turn her head in every direction without pain (Fig. 2). Interestingly, her severe menopausal symptoms were also relieved completely after 1 week of oral intake of Kanzo-to extract, as described in case 1 above. No adverse effects of Kanzo-to extract were observed in this case either.

Discussion

FSS is an idiopathic disease characterized by disability of the shoulder/cervical joints. Various treatments have been reported for FSS, including intraarticular steroid or morphine injections [1-4], distension and manipulation under local or generalized anesthesia [5, 6], distension arthrography [7, 8], acupuncture [9], and nerve block [10]. However, no specific treatment for a complete cure of FSS has been reported. This report may be the first to show Kanzo-to extract as a possible curative medicine for FSS. Most interestingly, not only the FSS but also the menopausal symptoms common to these two patients were completely relieved after oral administrations of Kanzo-to extract. These facts suggest that their menopausal symptoms may have been caused by FSS or that a common cause existed for the FSS and menopausal

Table. — Effects of Shakuyaku-kanzo-to extract and Kanzo-to extract on shoulder stiffness/pain and frozen shoulder in Patient 1.

Herbal medicine	Appearance of effect	Duration of effect	Effect on shoulder pain	Effect on FSS
Shakuyaku-kanzo-to 5 g p.o. (Tsumura)	25-30 min	3-6 hours	partially relieved	none
Kanzo-to 2 g p.o. (Kanebo)	50-60 min	6-8 hours	completely relieved	thawed

symptoms. The remarkable effects of Kanzo-to extract on the two patients were observed within several days. Adverse effects of Kanzo-to extract have been reported only rarely and were not found in our two patients. Considering these two cases, we may try Kanzo-to extract early on in other cases of FSS.

Herbal medicines have been used traditionally and widely in Japan, Korea, and China for centuries. They are often reported to be remarkably curative for diseases that have never been relieved by western medicines. However, the pharmacological mechanisms of such herbal medicines are seldomly analyzed scientifically. It is very difficult to investigate their mechanisms in vivo because herbal medicines are combined prodrugs and their effects are often affected by the intestinal bacterial flora, diet, and other individual factors. Kanzo-to extract is composed of 100% w/w Kanzo and is sometimes used in Japan for gastralgia or pharyngodynia. No one has reported the effects of Kanzo-to extract on FSS. Kanzo is the root and stolon of *Glycyrrhiza uralensis* Fischer, *Glycyrrhiza glabra* Linne, or other species of the same genus (Leguminosae). Shakuyaku is the root of *Paeonia lactiflora* Palla or allied plants (Paeoniaceae). Shakuyaku-kanzo-to extract, which comprises a 50% w/w Kanzo-derived component and a 50% w/w Shakuyaku-derived component, is used often in Japan especially for dysmenorrhea, gastralgia, and myalgia. There have been some pharmacological in vivo studies of Kanzo; glycyrrhizin, a major component of Kanzo; and glycyrrhetic acid, a metabolite of glycyrrhizin. Kanzo has been reported to suppress phospholipase A2 in human myometrial [11] and endometrial [12] tissues, which suppresses production of prostaglandins and is thought to be a mechanism by which Shakuyaku-kanzo-to reduces dysmenorrhea and gastralgia. Kanzo is also reported to suppress pro-

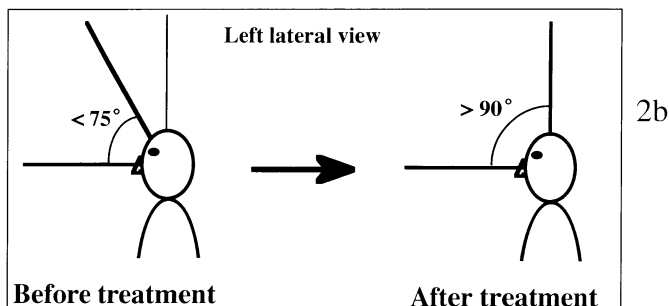
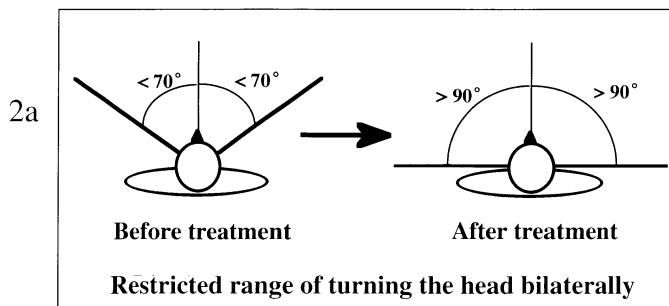


Figure 2. — Effects of Kanzo-to extract (2 g/day) on frozen neck in Patient 2.

duction of leukotriens in rat basophilic leukemia cells [13] and production of platelet activating factor (PAF) in human neutrophils [14]. Moreover, Kanzo, glycyrrhizin, and glycyrrhetic acid activate aromatase activity directly in ovarian granulosa cells and decrease serum testosterone levels [15, 16]. Therefore, Shakuyaku-kanzo-to extract has been used often in Japan for patients with polycystic ovary syndrome and anovulation with hyperandrogenemia [17-19]. Glycyrrhetic acid is also reported to inhibit 17- β -hydroxysteroid dehydrogenase in Leydig cells in testes and to decrease serum testosterone levels [20]. However, the mechanism by which our two FSS patients were cured is unknown. Since neither the prostaglandin synthesis inhibitor nor Shakuyaku-kanzo-to extract reduced FSS in patient 1, the curative mechanism of Kanzo-to extract on FSS may not be suppression of prostaglandin production. Because we did not find any significant change in serum LH, FSH, and estradiol before and after administration of Kanzo-to extract in patient 1 (data not shown), we think it unlikely that the curative mechanism was an endocrinological effect.

Both Shakuyaku-kanzo-to extract and Kanzo-to extract seemed to be very efficacious against the shoulder pain in patient 1, however Kanzo-to extract but not Shakuyaku-kanzo-to extract was efficacious against the restricted shoulder motion. The effects of herbal medicines on the patient's shoulder pain were quite different. The effects of Shakuyaku-kanzo-to extract appeared within 25-30 min and relieved the shoulder pain partially. However, the effects of Kanzo-to extract appeared within 50-60 min after oral intake and alleviated the shoulder pain completely. The effect of Shakuyaku-kanzo-to extract appeared earlier than that of Kanzo-to extract but was weaker and shorter-lived (summarized in Table). According to the manufacturer's specifications, 5 g of Shakuyaku-kanzo-to extract (Tsumura Co.) contains components derived from 4 g of Kanzo whereas 2 g of Kanzo-to extract (Kanebo Ltd.) contains components derived from 2.7 g of Kanzo. Five grams of Shakuyaku-kanzo-to extract is considered to have a greater Kanzo-derived component than 2 g of Kanzo-to extract. This suggests that Shakuyaku in Shakuyaku-kanzo-to inhibited the curative effect of Kanzo for FSS. If the mechanisms of Kanzo-to extract for FSS are made clear in the future, the pathogenesis of FSS in menopausal women might also become clear. Kanzo-to may be a medicine worth being tried against FSS in patients outside east Asia.

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Address reprint requests to:
TETSUJI TANAKA, M.D., Ph.D.
Assistant Professor
Department of Obstetrics & Gynecology
Osaka City University Medical School
1-4-3 Asahi-machi, Abeno-ku,
Osaka 545-8585 (Japan)