

Recent Japanese Research on Popular Chinese Herbal Formulas (Kampo) Part II

Compiled By Dan Wen, MD.

Rikkunshi-to (*Liu Jun Zi Tang*): A Chinese Herbal Formula for Common Gastrointestinal Problems

Enhance gastric motility in post-operative dyspeptic children

Yagi M, et al at Niigata University Graduate School of Medical and Dental Science evaluated the effect of Rikkunshi-to on the gastric myoelectric activity in post-operative dyspeptic patients, whose symptoms persisted for over 1 year after gastrointestinal surgery. Electrogastrography (EGG) recordings were performed to calculate the biomechanical parameters on the dominant peak frequency (DPF). Eight pediatric patients with dyspeptic symptoms after gastrointestinal surgery were examined and six age-matched children without any dyspeptic symptoms were used as controls, and they were compared with nine age-matched children without any dyspeptic symptoms after gastrointestinal surgery as subcontrols. All patients exhibited symptomatic relief after the administration of Rikkunshi-to, and the mean symptom score decreased significantly after the treatment of Rikkunshi-to over a 1-month period ($P < 0.0001$). The power ratio (PR) of EGG exhibited a significant increase after therapy ($P < 0.05$). However, there was a significant difference in the PR between the controls and subcontrols ($P < 0.05$). An abnormal gastric electrical activity therefore seems to be an important factor in the pathophysiology of post-operative dyspeptic children. The coordinating and stimulating effect of TJ-43 on the gastric myoelectric activity therefore seems to play an important role in the reduction of dyspeptic symptoms. (*Pediatr Surg Int.* 2004 9)

Increase levels of somatostatin and gastrin in human plasma

Rikkunshi-to has been used to treat chronic hypofunctions of the gastrointestinal tract. The effects of Rikkunshi-to on the plasma levels of gut-regulated peptide (somatostatin, motilin, gastrin, and vasoactive intestinal peptide (VIP)) levels were studied in healthy subjects. A single oral administration of Rikkunshi-to caused significant increases in plasma somatostatin and gastrin levels at 60 to 240 min compared with a placebo group. On the other hand, this medicine showed

no effects on motilin and VIP levels. In conclusion, these results might indicate that the pharmacological action of Rikkunshi-to is closely related to changes in somatostatin- and gastrin-immunoreactive substance levels. (*Biol Pharm Bull.* 2001 Jul;24(7):841-3.)

Promote adaptive relaxation in isolated guinea pig stomachs.

Some patients with dysmotility-like functional dyspepsia present impaired reservoir functions such as gastric adaptive relaxation. A traditional Chinese herbal medicine, Liu-Jun-Zi-Tang, has been identified as an effective drug against dyspeptic symptoms and is widely used for therapy in such patients. In this study, we examined the effects of this drug on the gastric adaptive relaxation in isolated guinea pig stomachs. The changes in intragastric volume and pressure were recorded in the presence of atropine and guanethidine. Gastric adaptive relaxation was induced by luminal distention. Liu-Jun-Zi-Tang (100 mg/ml) induced gastric adaptive relaxation at a lower intragastric pressure and increased the % volume of the gastric adaptive relaxation and the absolute intragastric volume. Metoclopramide (2 mg/ml), trimebutine (6 mg/ml) and cisapride (2 mg/ml) did not affect gastric adap-

Inside this issue:

- **Rikkunshi-to (*Liu Jun Zi Tang*): A Chinese herbal formula for common gastrointestinal problems**
- **Kampo herbal formulas for women's health**
- 1. **Toki-shakuyaku-san (*Dang Gui Shao Yao San*)**
- 2. **Keishi-bukuryo-gan (*Gui zhi fu ling wan*)**
- 3. **Kami-shoyo-san (*Jia Wei Xiao Yao San*)**

tive relaxation. It was inhibited by means of the incubation of the stomach with NG-nitro-L-arginine (100 microM). Liu-Jun-Zi-Tang (100 mg/ml), but not gastroprokinetics overcame the effect of NG-nitro-L-arginine. These results suggested that Liu-Jun-Zi-Tang promoted gastric adaptive relaxation. This effect might, at least in part, contribute to the symptom relief in patients with functional dyspepsia. (Drugs Exp Clin Res. 1999;25(5):211-8.)

Gastroprotection by Rikkunshi-to (Liu-Jun-Zi-Tang)

Liu-Jun-Zi-Tang (TJ-43) was examined for its mechanism of action in rats. TJ-43 significantly inhibited gastric mucosal damage caused by absolute ethanol at doses over 500 mg/kg in a dose-dependent way. Pretreatment with indomethacin or with N-ethylmaleimide did not affect the gastroprotective effect of TJ-43. However, pretreatment with NG-nitro-L-arginine partially but significantly reversed the protective effect of this drug. These findings suggest that the gastroprotective effect of TJ-43 occurs partly through nitric oxide but not through prostaglandins or sulfhydryls. (Drugs Exp Clin Res. 1999;25(5):207-10.)

Kampo herbal formulas for women's health

Toki-shakuyaku-san (*Dang Gui Shao Yao San*)

A Strong Anti-dysmenorrheal Therapy Using Toki-shakuyaku-san and Shakuyaku-kanzo-to

Tanaka T. at Wakayama Medical University reported a protocol for treatment of dysmenorrhea using two Japanese herbal medicines, Shakuyaku-kanzo-to (SK, Shao Yao Gan Cao Tang) and Toki-shakuyaku-san (TS). The protocol is referred to as "SK/TS cyclic therapy", in which the herbs are administered alternately within the menstrual cycle. All of the 17 dysmenorrhea patients including recurrent endometriotic and adenomyotic patients after treatment with gonadotropin-releasing hormone agonists or danazol, obtained complete relief (CR) 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. The SK/TS cyclic therapy can be a conservative antidysmenorrhea therapy for endometriotic and adenomyotic patients who desire pregnancy. (Clinical & Experimental Obstetrics & Gynecology. 30(2-3):95-8, 2003.)

Patient No.	Causes of Dysmenorrhea	Age	Cycle	Result
1	Endometriosis. Recurrence after GnRH α therapy	32	10	CR
2	Endometriosis. Recurrence after GnRH α therapy	26	14	CR
3	Endometriosis. Recurrence after GnRH α therapy	46	12	CR
4	Endometriosis. Recurrence after GnRH α therapy	36	8	CR
5	Endometriosis. Recurrence after GnRH α 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

Improving anemia associated with uterine myoma

Akase T. et al at Showa Pharmaceutical University of Tokyo have prospectively studied and compared the usefulness of Toki-shakuyaku-san and an oral iron preparation in the treatment of hypochromic anemia associated with uterine myoma. The study subjects consisted of 25 patients who were diagnosed as having hypochromic mild to moderate anemia associated with menorrhagia attributable to uterine myoma. They were divided into the Toki-shakuyaku-san group (n = 10) and the oral iron group (n = 15). The blood counts, subjective symptoms, and occurrence of side effects after oral administration of either preparation were monitored for 4 and 8 weeks in these subjects. In regard to the blood counts and improvements of the laboratory parameters of anemia, while marked improvement was observed in the oral iron group, no sig-

“The SK/TS cyclic therapy can be a conservative anti-dysmenorrhea therapy for endometriotic and adenomyotic patients who desire pregnancy.”

“Keishi-bukuryo-gan improves hot flash possibly by affecting plasma CGRP level.”

nificant improvement was noted in the Toki-shakuyaku-san group. On the other hand, in terms of improvement of the signs and symptoms of anemia, such as facial pallor, spoon-shaped nails and dizziness, the latter group also showed significant improvement. In addition in the Toki-shakuyaku-san group, resolution of symptoms such as hypermenorrhea, dysmenorrhea, feeling cold, dizziness, headache and shoulder stiffness was also noted. While side effects were encountered in 80.0% of patients in the oral iron group, no significant side effects were observed in the Toki-shakuyaku-san group. From these findings, it is considered that Toki-shakuyaku-san may be useful for resolving the symptoms of mild or moderate anemia associated with uterine myoma. (Yakugaku Zasshi - Journal of the Pharmaceutical Society of Japan. 123(9):817-24, 2003 Sep.)

Improving Luteal Insufficiency in Fecund Women.

Usuki S., et al. at the University of Tsukuba has studied the effect of tokishakuyakusan in women with luteal insufficiency and in women with normal menstrual cycles. Luteal insufficiency was determined by daily measurement of basal body temperature and plasma progesterone levels. Tokishakuyakusan improved luteal insufficiency. Furthermore, the effects of tokishakuyakusan on prolactin, gonadotropins, steroids, angiotensin II, ANP and renin levels in the blood of women with normal menstrual cycles were studied, as were the herbal medicine's effects on estrogens, pregnenediol and LH in the urine of the same women. Tokishakuyakusan had no adverse effect on hormonal levels in either blood or urine. Furthermore, no clinical side effects were detected. These results suggest that tokishakuyakusan improves luteal insufficiency in women but does not affect the hormonal levels of women with normal menstrual cycles. (American Journal of Chinese Medicine. 30(2-3):327-38, 2002.)

Relief Menopausal Symptoms Such as Hot Flash without Affecting Estradiol Levels

Tanaka T at Osaka City University has studied the therapeutic effects of certain Japanese herbal medicines on menopausal symptoms induced by gonadotropin-releasing hormone agonist therapy 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. (Clinical & Experimental Obstetrics & Gynecology. 28(1):20-3, 2001.)

Keishi-bukuryo-gan (*Gui Zhi Fu Ling Wan*)

Treatment of Menopausal Hot Flash

OBJECTIVES: The purpose of this study is to investigate relationship of menopausal hot flash and calcitonin gene-related peptide (CGRP). Furthermore, this study evaluated the effect of the Japanese herbal (kampo) medicine Keishi-bukuryo-gan from the aspect of CGRP regulation. **METHODS:** Plasma CGRP and vasoactive intestinal peptide (VIP) levels were measured during hot flash and CGRP reactivity was studied by cold load test in subjects with/without hot flashes. The effect of Keishi-bukuryo-gan was assessed in comparison with plasma CGRP level. **RESULTS:** Only plasma CGRP but not VIP significantly elevated at the occurrence of hot flash ($P=0.002$). Stress by cold load significantly enhanced the over-secretion of CGRP in subjects with flash compared with those without flash ($P=0.003$) 3 min after the load. Keishi-bukuryo-gan decreased plasma CGRP level in subjects with hot flash. **CONCLUSIONS:** CGRP but not VIP was mainly related to the occurrence of hot flash. Keishi-bukuryo-gan, Japanese herbal medicine, improves hot flash possibly affecting plasma CGRP level. (Maturitas. 45(3):199-204, 2003 Jul 25.)

Treatment of Endometriosis Is Involved with Anti-endometrial IgM autoantibodies

Japanese herbal medicines are usually the third most popular choice among medicines for treatment of endometriosis in Japan. This traditional therapy is used to improve various signs and symptoms of endometriosis without decreasing serum estradiol levels or causing menstrual disorders. We used flow cytometry to examine and compare the effects of the Kampo therapy and danazol on anti-endometrial humoral immunity. Autoantibodies against endometrial epithelial cell lines and endometrial stromal cells were detectable in all the examined sera of men and women irrespective of the presence of endometriosis. Moreover, no significant increase in anti-endometrial antibodies was found in endometriotic patients. Anti-endometrial antibodies included Ig-gamma chain, Ig-mu chain, Ig-kappa chain, and Ig-lambda chain indicating polyclonal B cell activation in the endometriotic patients. Absorption

tests of nonspecific antibodies with cervical cancer cells or ovarian cancer cells revealed that endometriotic patients had higher levels of endometrium-specific autoantibodies than did non-endometriotic healthy women. IgM fractions from endometriotic patients and healthy women differed in their effect on growth of endometrial adenocarcinoma cells. Therapy with the herbal compounds Keishi-bukuryo-gan but not danazol therapy, gradually decreased the tissue-specific anti-endometrial IgM antibody levels. These results indicate that tissue-specific anti-endometrial IgM may be a useful therapeutic marker for endometriotic patients treated with Keishi-bukuryo-gan and that endometrial tissue-specific immune disorders play specific roles in the pathogenesis or development of endometriosis. (Clinical & Experimental Obstetrics & Gynecology. 27(2):133-7, 2000)

Kami-shoyo-san (*Jia Wei Xiao Yao San*)

Treatment of Panic Disorder with Kami-shoyo-san and Hange-koboku-to (Ban Xia Hou Po Tang)

Mantani N. et al. at Toyama Medical and Pharmaceutical University reported successful treatment of four cases of panic disorder with Kami-shoyo-san and Hange-koboku-to (Ban Xia Hou Po Tang). These four patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for panic disorder with agoraphobia. The Kampo medicine Kami-shoyo-san relieved panic attacks, anticipatory anxiety and agoraphobia in two patients, and Hange-koboku-to relieved these symptoms in the other two patients. The patients in whom Kami-shoyo-san was effective were older and complained of more symptoms than those in whom Hange-koboku-to was effective. These Kampo medicines may be useful as additional or alternative treatments for panic disorder. (Psychiatry & Clinical Neurosciences. 56(6):617-20, 2002 Dec.)

Treatment of Premenstrual Dysphoric Disorder

Kami-shoyo-san has been used to treat irregularity of menstruation and anxiety involved with a menstrual cycle. Six untreated women with premenstrual dysphoric disorder (PMDD) diagnosed by the research criteria of DSM-IV whose ages ranged from 29 to 48 years old, were treated with Kami-shoyo-san at a daily dose of 7.5 g (2.5 g three times daily, orally) for six menstrual cycles. Their rating scores of CGI (Clinical Global Impressions Scale), GAF (Global Assessment of Functioning Scale), Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scales at the late luteal phase, before the treatment of Kami-shoyo-san and six menstrual cycles after the administration of Kami-shoyo-san were assessed. Six menstrual cycles after the administration of Kami-shoyo-san, at the late luteal phase, CGI scores (4.3 ± 0.5 to 2.7 ± 0.5), HAM-D scores (18.0 ± 3.2 to 6.0 ± 3.7), and HAM-A scores (21.8 ± 6.1 to 8.3 ± 4.6) decreased, and GAF scores improved (59.0 ± 5.6 to 77.0 ± 6.7). All of the patients did not fulfill the research criteria for PMDD, and their severity of depression and anxiety at the late luteal phase remitted. No adverse events occurred with Kami-shoyo-san administration in any patient. The exact mechanism underlying this effect is unknown, though bupleuri radix of Kami-shoyo-san is shown to have inhibitory effects on central nervous system. In summary, our results suggest that Kami-shoyo-san may be effective for PMDD, without adverse events. (Journal of Clinical Psychopharmacology. 22(4):442, 2002 Aug.)

Mechanism of Anxiolytic Effect of Kami-Shoyo-San: Neurosteroid Synthesis

Mizowaki M. et al. at the Kitasato Institute assessed the anxiolytic effect of Kami-Shoyo-San (Jia wei xiao yao san) by the social interaction (SI) test in male mice. Acute administration of Kami-Shoyo-San (25-100 mg/kg, p.o.), as well as the gamma-aminobutyric acid/benzodiazepine (GABA(A)/BZP) receptor agonist diazepam (1-3 mg/kg, i.p.), dose dependently increased the SI time, respectively. The GABA(A) receptor antagonist picrotoxin blocked the effects of Kami-Shoyo-San and diazepam. Kami-Shoyo-San-induced SI behavior was significantly blocked by the GABA(A)/BZP receptor inverse agonist Ro 15-4513 and the GABA(A)/BZP receptor antagonist flumazenil. In addition, 5alpha-reductase inhibitor finasteride potentially blocked the effect of Kami-Shoyo-San without attenuating the basal level by itself. These findings suggest that Kami-Shoyo-San shows the anxiolytic effect through the neurosteroid synthesis followed by GABA(A)/BDZ receptor stimulations. (Life Sciences. 69(18), 2001,21.)

Dan Wen has nearly 20-year experience in clinical and laboratory research on humans and animals in China and America in the use and integration of Chinese herbal and Western medicines, including a 3-year research fellowship in gastroenterology at Mayo Clinic. His research at Washington University School of Medicine on absorption of vitamin B₁₂ has been supported by a research grant from NIH. He has also published numerous research papers. Currently he is the President of Honso USA Inc., headquartered in Phoenix Arizona, where the pharmaceutical grade Japanese Kampo products are distributed.

The Newsletter is for professional and educational use only. It is only intended to provide an exchange of information. The statements in the Newsletter have not been evaluated by the Food and Drug Administration. The products mentioned are not intended to diagnose, treat, cure or prevent any disease.