Maturitas 62 (2009) 146–152

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine

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ARTICLE INFO

Article history:
Received 18 March 2008
Received in revised form
21 November 2008
Accepted 11 December 2008

Keywords:
Interleukin-6
Psychological symptoms
SSRI
Japanese traditional medicine
Midlife women

ABSTRACT

Objective: The aim of the present study was to compare the effects on serum cytokine concentrations of paroxetine, a selective serotonin re-uptake inhibitor, and kamishoyosan, a Japanese traditional medicine, in midlife women with psychological symptoms.
Methods: Seventy-six women with psychological symptoms such as anxiety and mild depression as menopausal symptoms were enrolled in this study. Thirty-eight women received oral administration of 10 mg paroxetine every day, and 38 women received oral administration of kamshoyosan every day for 6 months. Overall climacteric symptoms were assessed using Greene's climacteric scale. Serum levels of cytokines were measured using a multiplexed human cytokine assay.
Results: Greene's total scores in both women treated with paroxetine and in women treated with kamishoyosan decreased significantly. Percentage decreases in Greene's total, psychological and vasomotor scores during the 6-month period in the paroxetine group were significantly greater than those in the kamishoyosan group. Serum IL-6 concentration in women treated with paroxetine decreased significantly. Serum concentrations of IL-8, IL-10, macrophage inflammatory protein (MIP)-1β and monocyte chemoattractant protein-1 in women treated with paroxetine decreased significantly. On the other hand, serum IL-6 concentration in women treated with kamishoyosan decreased significantly, but other serum concentrations did not change significantly.
Conclusion: Decrease in IL-6 concentration may be involved in the mechanism of the actions of both paroxetine and kamishoyosan in women with psychological symptoms, and IL-6 may therefore be useful as a marker of treatment. The action of paroxetine may also be associated with decreases in IL-8, IL-10, MIP-1β.

1. Introduction

In midlife women during the menopausal transition, psychological symptoms such as anxiety and mild depression as well as vasomotor symptoms have been observed as menopausal symptoms. A selective serotonin reuptake inhibitor (SSRI) has been used to treat depression in women, but adverse reactions such as nausea and headache have been observed in women treated with SSRI [1].

In Japan, various Japanese traditional medicines have been used for treating women who complain of menopausal symptoms. Kamishoyosan (Jia-wei-xiao-yao-san) is one of the formulae used for treatment of psychological symptoms such as anxiety, depression and irritability in menopausal women [2,3]. Recently, it has been reported that women with premenstrual dysphoric disorder were successfully treated with kamishoyosan [4]. Kamishoyosan consists of the following 10 medical herbs: Bupleurum root, Peony root, Atractylodis lanceae rhizome, Angelica root, Hoelen, Gardenia fruit, Moutan bark, Glycyrrhiza root, Ginger rhizome and Mentha herb. It is thought that kamishoyosan acts on the central nervous system, but the mechanism of the action of kamishoyosan has not been fully elucidated.

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doi:10.1016/j.maturitas.2008.12.007

Cytokines are involved in various functions of the central nervous system. It has been reported that circulating cytokines are dysregulated in major depression [5]. Plasma interleukin (IL)-6 concentration has been reported to be increased in major depressive disorders [6,7]. Levels of mitogen-induced cytokines such as IL-1β, IL-2, IL-10 and interferon (IFN)-γ have also been reported to be high in patients with major depression [8]. In midlife women with depression as a menopausal symptom, plasma IL-6 concentration was found to be increased [9]. We also reported that serum concentrations of IL-6, IL-8 and IL-10 were high in midlife women with psychological symptoms [10]. On the other hand, it has been reported that decreases in serum concentrations of IL-6 and tumor necrosis factor (TNF)-α were observed in depressed patients treated with SSRI [11,12]. Ushiroyama et al. reported that plasma TNF-α concentration was increased in depressed menopausal women treated with kamishoyosan [3]. However, the changes in cytokines in women treated with paroxetine and kamishoyosan have not been fully elucidated.

To date, it has been difficult to detect low levels of circulating cytokines in serum of healthy women. Recently, a multiplexed cytokine assay for measurement of serum concentrations of cytokines has been developed, and the use of this assay has enabled simultaneous measurements of low levels of various cytokines in serum of healthy subjects [13,14].

In the present study, we compared the effects of paroxetine and kamishoyosan on serum cytokine concentrations in midlife women with psychological symptoms using a highly sensitive multiplexed cytokine assay.

2. Subjects and methods

2.1. Subjects

The subjects of this study were recruited from patients visiting the outpatient clinic of the Department of Obstetrics and Gynecology, Tokushima University Hospital. Seventy-six women who had complained of psychological symptoms such as anxiety and mild depression as menopausal symptoms were enrolled in this study between November 2005 and October 2007. Informed consent for participation in this study was obtained from each woman. The Ethics Committee of Tokushima University Hospital approved the study. Women with major depression were excluded. Reviews of medical histories and the results of physical examinations and blood chemistry tests showed that all of the women were in good health. None of the subjects had taken any medication known to influence the immune system for at least 1 year. Subjects suspected of having infectious diseases, inflammatory disorders, malignancy or autoimmune diseases, of being undernourished, or of abusing alcohol or drugs were excluded according to the SENIEUR protocol [15]. Seven premenopausal women had regular menstruation and 32 perimenopausal women had experienced alterations in menstrual frequency and/or flow in the 12 months preceding entry into the study, and natural menopause had occurred in 37 women at least 12 months before entry into the study. Eligible women were randomly assigned in open, parallel-group fashion to a paroxetine group or kamishoyosan group. Thirty-eight women received oral administration of 10 mg paroxetine (Glaxo) every day and 38 women received oral administration of 7.5 g kamishoyosan (Tsumura Co., Tokyo, Japan) every day for 6 months. Climacteric symptoms were assessed using Greene's climacteric scale [16]. Compliance was assessed by pill count or sheet count, and side effects were ascertained by questionnaires at 4-week intervals. Venous blood samples were drawn into tubes between 8 a.m. and 10 a.m. after a 12-h fasting before and at 6 months of treatment. Samples obtained were frozen at −70 °C until use for analysis.

2.2. Preparation of herbal drugs

Kamishoyosan is composed of 10 medical herbs: 3 g of Bupleurum root, Peony root, Atractylodis lanceae rhizome, Japanese Angelica root, and Hoelen; 2 g of Gardenia fruit and Moutan bark; 1.5 g of Glycyrrhiza root and 1 g of Ginger rhizome and Mentha herb. Kamishoyosan used in the present study was prepared as a spray-dried powder from hot water extract and obtained from Tsumura Co. Ltd. (Tokyo, Japan).

2.3. Measurement of serum cytokine concentrations

Serum concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, TNF-α, IFN-γ, macrophage inflammatory protein (MIP)-1β and monocyte chemotactic protein (MCP)-1 were measured by using a Bio-Plex human multi-plex cytokine assay kit (Bio-Rad Laboratories, Hercules, CA, USA) as previously reported [14]. The intra- and inter-assay coefficients of variation were 2.0–7.0% and 5.2–16.1%, respectively. The sensitivity levels were 1.1 pg/ml for IL-2, IL-6 and MIP-1β, 0.5 pg/ml for IL-4, IL-7 and IL-8, 0.8 pg/ml for IL-1β and IL-5, 0.9 pg/ml for IL-10, 19.3 pg/ml for IFN-γ, 3.0 pg/ml for TNF-α and 6.7 pg/ml for MCP-1.

2.4. Measurements of concentrations of estradiol and FSH

Serum estradiol concentration was measured by a two-site immunoenzymometric assay using a commercially available kit (TOSOH Co., Tokyo, Japan). The intra- and inter-assay coefficients of variation were 4–9% and 6–9%, respectively, and the detection limit was 20 pg/ml. Serum FSH concentration was measured by an immunoradiometric assay using a commercially available kit (TFB Co., Tokyo, Japan). The intra- and inter-assay coefficients of variation were 3–4% and 3–4%, respectively, and the detection limit was 1.0 IU/l.

2.5. Analysis of kamishoyosan by HPLC

Kamishoyosan was extracted with 20 ml of methanol under ultrasonication for 30 min. The solution was filtered and subjected to treatment with an alumina cartridge (Bond Elute Co. Ltd.). Elution provided the alkaloid fraction. The methanol solution and the alkaloid fraction were tested. HPLC with an LC-10AD pump (Shimazu, Tokyo, Japan) and SPD-M10A absorbance detector was performed using a TSK-GEL ODS-80TM column (150 mm × 4.6 mm). The effluent from the column was monitored at 254 nm with a UV detector.

2.6. Statistical analysis

Based on results of the previous study [17], sample size was estimated to detect at least 20% change in levels of cytokines and chemokines after administration with 80% power at the 0.05 level of significance. We defined the values below the detection limit as half of the detection limit in further analyses. Differences between the paroxetine group and the kamishoyosan group in subject's characteristics, baseline serum hormonal concentrations and Greene's scores and percentage changes in Greene's scores were analyzed by an unpaired *t*-test, and values are presented as means ± standard deviations. Baseline serum cytokine levels, which were not normally distributed, are presented as medians with 10th and 90th percentile ranges, and significance of those values was evaluated by the non-parametric Wilcoxon rank sum test. Changes by treatments in Greene's scores were analyzed by Student's paired *t*-test, and changes by treatments in serum cytokine levels were analyzed by the non-parametric Wilcoxon signed-rank test. The relationship among continuous variables was determined by using Spearman's rank order analysis. *p* values less than 0.05 were considered to be