Fluoxetine in the treatment of premenstrual syndrome

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Abstract

Background: Premenstrual syndrome (PMS) is defined as the disabling and cyclic occurrence of emotional and behavioral symptom complex during the latter half of the menstrual cycle. Although its etiology is unknown, it has been speculated that premenstrual syndrome is linked to a deficiency of central serotonergic activity. Method: The study consisted of a double-blind, placebo controlled trial of fluoxetine at a dose of 20 mg/day or placebo for three menstrual cycles. The 440 women who appeared to meet the eligibility criteria were instructed to record the 'Calendar of Premenstrual Experiences' (CPE) scale for two complete menstrual cycles. Of 410 women who successfully completed two cycles of recording their symptoms daily only 35 met the criteria for PMS. These criteria included psychiatric interviews which were made before treatment. Thirty-five PMS patients were randomized into placebo or fluoxetine treatment groups. Results: Our study suggests that fluoxetine at a dose of 20 mg per day was significantly superior to placebo in alleviating the symptoms of PMS. The most common side effects were gastrointestinal irritability (15%), insomnia (11%) and sexual dysfunction (8.5%). Conclusion: Fluoxetine is an effective and well-tolerated drug and appears to have considerable promise in treating a range of symptoms in women with PMS. © 1997 Elsevier Science Ireland Ltd.

Keywords: Premenstrual syndrome; Fluoxetine; Calendar of Premenstrual Experiences Scale

1. Introduction

Premenstrual syndrome (PMS) is defined as the disabling and cyclic recurrence of a combination of behavioral and physical symptoms that occur in the luteal phase of the menstrual cycle following a period of time entirely free of symptoms. The most frequent symptoms encountered include abdominal bloating, irritability, anxiety, depression, fatigue, crying spells, affective lability, hypersomnia or insomnia, breast tenderness and thirst and appetite changes that last for 7–10 days of the cycle [1].

In 1994, The American Psychiatric Association published the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and renamed the syndrome as premenstrual dysphoric disorder (PMDD). The incorporation of specific diagnostic criteria, as proposed by the DSM-IV, into clinical practice is important, because it increases the likelihood that clinicians will inquire about menstrual cycle phase-related symptoms and identify the diagnostic process as longitudinal and not cross-sectional (given the time-oriented rather than symptom-oriented nature of the diagnosis) [2]. The diagnosis must be confirmed prospectively over at least two consecutive menstrual cycles by rating scales [3–6].

Premenstrual symptoms occur in up to 80% of reproductive-age women [7] but on the basis of strict criteria [8] and with the exclusion of other pathologies, the true incidence of PMS varies between 2.5 and 10% [9]. Although the exact etiology is unknown it is assumed that PMS is a complex psychoneuroendocrine disorder [10]. Dietary and nutritional factors, stress and personality factors, ovarian steroids and metabolites and neurotransmitters are all accused in the pathogenesis of PMS. Fluctuations in the gonadal steroids estrogen and progesterone have been associated with changes in sev-
eral neurotransmitter systems. Of all of the neurotransmitters studied to date, increasing evidence suggests that serotonin (5-hydroxytryptamine, 5-HT) may be important in the pathogenesis of PMS [11–13]. As known serotonin is a neurotransmitter derived from the aminoacid l-tryptophan and has been implicated in various affective and emotional disorders. Premenstrual carbohydrate cravings, affective lability, sleep disturbances, impulsivity and increased carbohydrate intake in patients with PMS suggest involvement with serotonin [14]. Whole-blood serotonin, imipramin binding and platelet serotonin uptake are decreased during the luteal phase of the menstrual cycle in women with PMS [15]. In addition, the serotonin metabolite, 5-hydroxyindoleacetic acid has been measured in urine across the menstrual cycle and found to be highest at the mid-luteal phase and lower in the late luteal phase [16]. The decreased serotoninergic activity that is found in the late luteal phase of the menstrual cycle may be implicated in many of the symptoms of PMS. A link between PMS and major depression is suggested by symptom overlap and by the observation that pre-existing depression is often aggravated just before menses [17].

Selective serotonin reuptake inhibitors (SSRIs) are represented by fluoxetine, sertraline, paroxetine and fluvoxamine. All of them block reuptake of serotonin and have minimal side effects on dopamine but fluoxetine differs from other SSRIs in its half life. It has a 2–3 day half life and it takes 3 weeks to reach steady state concentration in blood whereas other SSRIs have a 16–22 h half life. In the present study, we evaluated the efficacy of fluoxetine in the treatment of premenstrual syndrome.

2. Materials and methods

The study consisted of a double-blind, placebo-controlled trial of fluoxetine at a dose of 20 mg/day or placebo for three menstrual cycles. Subjects were selected (as detailed below) from 500 factory workers in the Kocaeli region who showed an interest in participating in the study. Careful screening was performed to control for three menstrual cycles and to continue to complete their CPE scales for the duration of the treatment. Post-treatment results were scored when the three treatment cycles had been completed. We determined the responder as those whose luteal phase score was less than 40. The statistical analysis was performed with the GraphPad InStat PC program (GraphPad Software, 1993).

3. Results

Both of the study groups were comparable in age, parity and pretreatment follicular and luteal phase scores as assessed by the baseline CPE scale (Table 1). Five patients were excluded during the trial, two from the placebo group and three from the fluoxetine group either because of protocol violation or through intolerable adverse effects of fluoxetine.

During the trial only 4 of 15 patients from the placebo group (mean difference, 9.08; t, 1.51; 95% confidence interval (CI) of the difference, -3.14–
Table 1
Pretreatment characteristics of PMS groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine (n = 18)</th>
<th>Placebo (n = 17)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean S.D.</td>
<td>S.E.M.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Age</td>
<td>30.6 7.48</td>
<td>1.76</td>
<td>31.7 7.42</td>
</tr>
<tr>
<td>Parity</td>
<td>1.94 1.16</td>
<td>0.27</td>
<td>1.94 1.14</td>
</tr>
<tr>
<td>Follicular phase score**</td>
<td>16.2 5.9</td>
<td>1.3</td>
<td>18.6 6.0</td>
</tr>
<tr>
<td>Luteal phase score**</td>
<td>62.3 14.6</td>
<td>3.4</td>
<td>67.3 16.8</td>
</tr>
</tbody>
</table>

NS, not significant (P > 0.05); s, significant (P < 0.001).
* P-value is determined by the two-tailed t test.
** Scores are assessed by the Calendar of Premenstrual Experiences scale.

21.31; two-tailed P-value, 0.139; considered not significant. unpaired t-test; the difference between the two S.D.s is not significant; P = 0.47) and 12 of 15 patients from the fluoxetine group (mean difference, 31.45; t, 7.14; CI 95%, of the difference, 22.47–40.43; two-tailed P-value less than 0.0001, considered extremely significant, unpaired t-test; the difference between the two S.D.s is not quite significant; P = 0.055) responded to treatment (Fig. 1). The post-treatment total luteal CPE scores of the fluoxetine group were seen to have decreased by 58% (the two-tailed P-value is less than 0.0001, considered extremely significant, Mann–Whitney test) whereas the decrease was only 23% in the placebo group (the two tailed P-value is 0.126, considered not significant, Mann–Whitney test). There was no significant difference between pre- and post-treatment follicular CPE scores (q = 1.713, P > 0.05, Tukey Kramer Multiple Comparisons Test). The use of fluoxetine was seen to improve not only behavioral and affective symptoms but also physical symptoms (Fig. 2).

During the trial, two patients from the fluoxetine group were discarded because of intolerable nausea and skin rash and five patients from this group experienced mild, transient side effects. The most common side effects were gastrointestinal irritability (15%), insomnia (11%) and sexual dysfunction (8.5%). Two patients from the placebo group experienced headache and dizziness not requiring any medication. Since the symptoms of PMS tend to be recurrent without treatment all of the patients were advised to continue fluoxetine therapy.

4. Discussion

Although its etiology is unknown, it has been speculated that premenstrual syndrome is linked to a deficiency of central serotoninergic activity. Our study suggests that fluoxetine at a dose of 20 mg per day was significantly superior to placebo in alleviating the symptoms of PMS. Our results support the findings of other studies [19–21]. Although there is evidence supporting the role of other antidepressants, anxiolytics and GnRH analogs in the treatment of PMS, the selective serotonin reuptake inhibitors are becoming the first line of therapy for PMS [22,10].

Although we only tested fluoxetine over three menstrual cycles, its efficacy and safety over a longer time period have been demonstrated [23]. Our trial encompassed 15 patients receiving fluoxetine but in the literature there are articles covering larger numbers [8]. Finally, fluoxetine is an effective and well-tolerated drug and appears to have considerable promise in treating a range of symptoms in women with PMS [8,10,19–23].
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References