Bromocryptine (Bromergon®, Lek) in the management of premenstrual syndrome

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Summary: The efficacy of bromocryptine (Bromergon®, Lek) was studied in a group of 21 women with premenstrual syndrome (PMS). To qualify for inclusion, the patients had to have a score of 20 or more on Casper's Analog Self-Rating Scale for Premenstrual Tension Syndrome completed during the last premenstrual week.

The study was designed as a double-blind, randomized, cross-over trial introduced by a wash-out cycle. Patients received Bromergon® in a daily dose of 5 mg from cycle day 10 to the onset of menstruation for two consecutive menstrual cycles, followed by two placebo cycles or vice versa. The subjects were instructed to complete the scale every three days from cycle day 3 to the onset of menstruation. A statistically significant improvement due to the administration of Bromergon® was observed in symptoms associated with overreactiveness to normal prolactin levels, i.e. abdominal tension, edema, weight gain and breast tenderness. Scores on the linear analog scale and physician's assessments differed regarding psychological symptoms. The investigators observed no difference in the presence of psychic symptoms in the treatment-free period, on Bromergon® therapy and during the administration of placebo. On the other hand, self-rating scores reflected an improvement in the presence of depression and irritability during Bromergon® treatment.

The results obtained suggest that Bromergon® may be a useful agent for the treatment of somatic symptoms associated with PMS, while it seems somewhat less effective in PMS cases where psychic symptoms are the major complaint.

Key words: Bromocryptine; Premenstrual syndrome.

INTRODUCTION

Premenstrual syndrome (PMS) is a common disorder in women of childbearing age.

According to Reid ([1]), PMS is a combination of distressing physical, psychological and behavioral changes, recurring cyclically in the luteal phase of the menstrual cycle with sufficient severity to produce a negative impact on interpersonal relationships and everyday activities.

The general physical symptoms included tension and edema of different parts of the body, breast tenderness, weight gain, headache, migraine, fatigue and nausea. Psychic symptoms are usually related to depressive states, fear, changes of mood, forgetfulness, aggressiveness and restlessness. Behavioral changes are manifested as various eating excesses (alcohol or sweets abuse), altered attitude to professional activities, enhanced or diminished libido, impaired intrafamilial relationships.

Various defects, including estrogen excess, progesterone deficit, fluid reten-

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tion, hyperprolactinemia, vitamin B_6 deficiency, hypoglycemia, prostaglandin deficiency or excess, autoimmune response to hormones, impaired opioid production, thyroid dysfunction, serotonin deficiency and psychic disorders have been postulated as possible causative agents for PMS ([2]).

Since breast tenderness (mastalgia and mastodynia) is one of the leading symptoms of PMS, the aim of this trial was to assess the effect of bromocryptine, a prolactin release inhibitor (Bromergon, Lek) on this and other symptoms associated with PMS.

The study was carried out on women with premenstrual syndrome using a double-blind cross-over protocol.

PATIENTS AND METHODS

Women with severe or moderate PMS symptoms as evidenced by a linear analog scale score of 20 or more on cycle days 24 and 27 were enrolled. Relatively regular menstrual cycles (23-35 days), an age between 20 and 45 years and normal or elevated prolactin levels were required to qualify for inclusion.

Grounds for exclusion were psychiatric or gynecologic disorders and concomitant use of other medications.

Clinical assessment of the efficacy of treatment

The women were asked to assess their symptoms on Casper's linear analog scale every three days throughout the cycle. The self-rating scale comprised the following items: irritability, depression, anger, headache, abdominal tension and breast tenderness, each rate from 0 (no symptoms) to 10 (very severe).

The general and local somatic and psychic symptoms were scored by the investigator from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe).

The study extended over 5 consecutive menstrual cycles and was divided into three study periods. During the first period (wash-out period) the subjects were asked to assess the severity of their symptoms while taking no medication. During the second period, which comprised two menstrual cycles, the patients were randomly assigned to receive either placebo or bromocryptine (Bromergon 1 tablet of 2.5 mg twice daily after meals) from cycle day 10 to the onset of menstruation. In the third study period the two test groups were crossed over, so that patients having received Bromergon switched to placebo and vice versa.

The study included 21 patients with symptom scores compatible with the diagnosis of PMS. Six patients were withdrawn in the course of treatment: three due to pregnancy occurring in the 2nd and 3rd study cycle and another three due to death of partner, hypotension and poor compliance. A total of 15 patients completed the study.

RESULTS

The results obtained were statistically analyzed by using the t-test, Friedman's Wilcoxon's and McNamara's tests.

Investigator's assessment

For the purposes of assessment, the PMS symptoms were divided into three groups. General somatic symptoms included assessment of fatigue, pain, thirst, occurrence of acne and body weight gain. Local somatic symptoms comprised headache, edema, abdominal tension, diplopia and mastodynia. The psychic symptoms checked included depression, anxiety, irritability, apathy, changes of mood, pessimism, retardation, diminshed libido, sadness and loss of interest.

A statistically significant difference in the presence and severity of general somatic symptoms was observed only for body weight gain prior and during Bromergon therapy (Fig. 1).

Analysis of local somatic symptoms (headache, diplopia, mastodynia) showed a statistically significant decrease in the incidence and severity of edema during Bromergon therapy compared with an increase on placebo (Fig. 2). Abdominal tension also significantly decreased on Bromergon compared with the treatment-free period (Fig. 3).

The incidence and severity of psychic symptoms did not change between the wash-out, active treatment and placebo period.

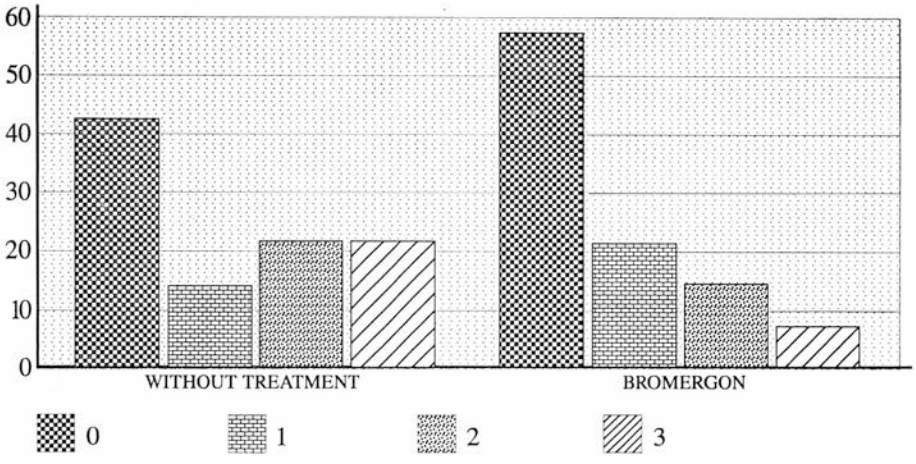

Fig. 1. — Increase in body weight (BW), estimated by physician (%): 1) without changes; 1) BW increase of 0.5 kg; 2) BW increase of 1 kg; 3) BW increase of 1.5 kg.

Linear analog scale scores

Each item on the linear analog scale received a double score, the first score refers to the measurement on the last premenstrual day, while the second is the mean value of three premenstrual measurements.

The mean score for irritability revealed a statistically significant decrease on Bromergon therapy in comparison with the treatment-free period (Fig. 4).

The scores for depression and abdominal tension also showed a definite decrease during Bromergon therapy. Breast tenderness, as the leading symptom of PMS, significantly decreased during the first cycle on Bromergon. On the other hand, in the first placebo cycle it significantly increased in comparison with the last premenstrual score and the mean of three consecutive premenstrual measurements. The mean score for breast tenderness was

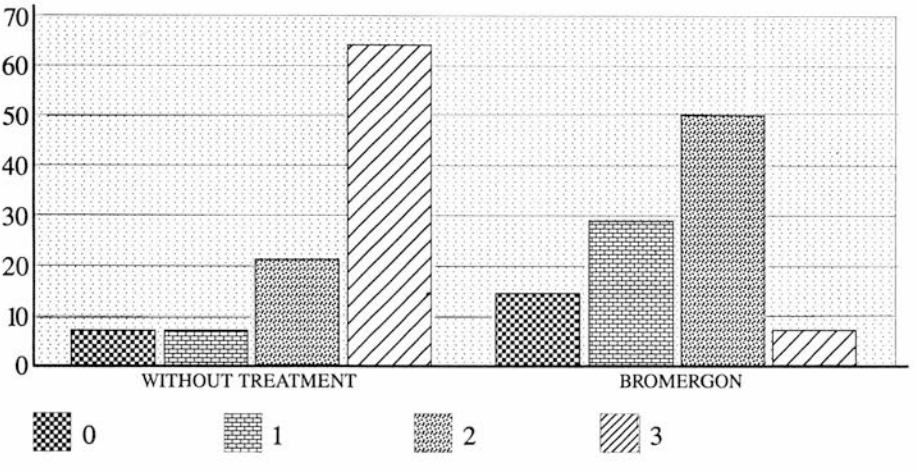

Fig. 2. — Decrease in severity and frequency of edema, estimated by physician (%).

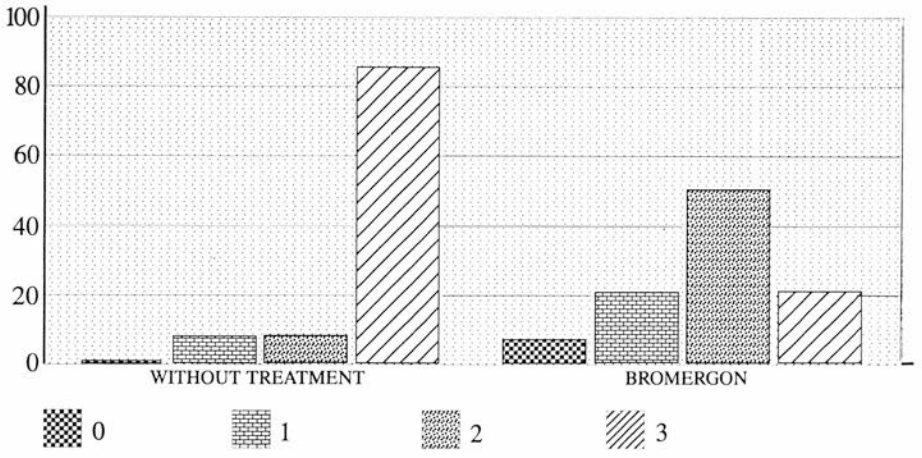

Fig. 3. — Decrease in abdominal tension, estimated by physician (%).

also significantly lower in the 2 cycle on Bromergon therapy in comparison with the treatment-free period (Fig. 5).

The scores for headache and anger showed no differences between the three study periods.

There were no statistically significant differences between pre- and post-treatment blood and urine tests.

Likewise, there were no statistically significant differences in prolactin levels prior to and on completion of treatment.

Adverse effects

In one patient Bromergon had to be discontinued during the first treatment cycle due to excessive hypotension. Other patients developed no adverse reactions.

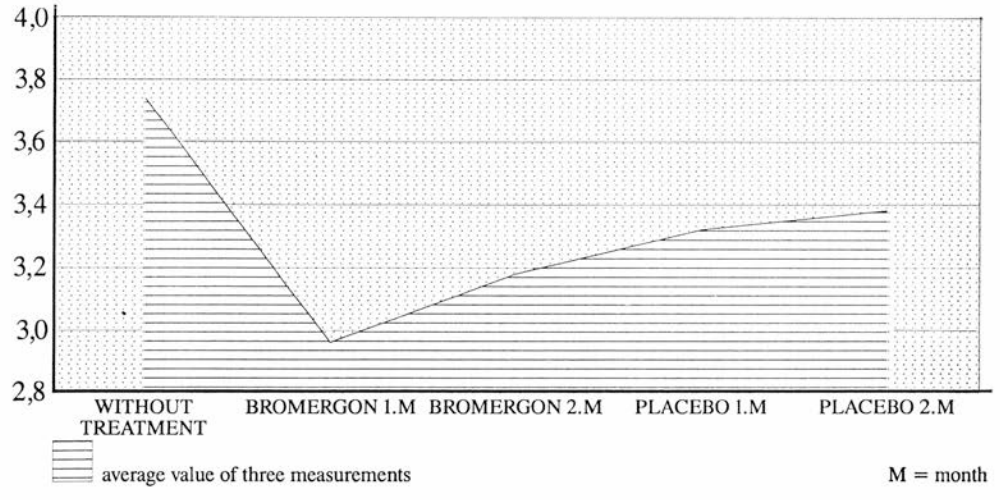

Fig. 4. — Irritability, estimated by linear analog scale one week before the onset of menstruation.

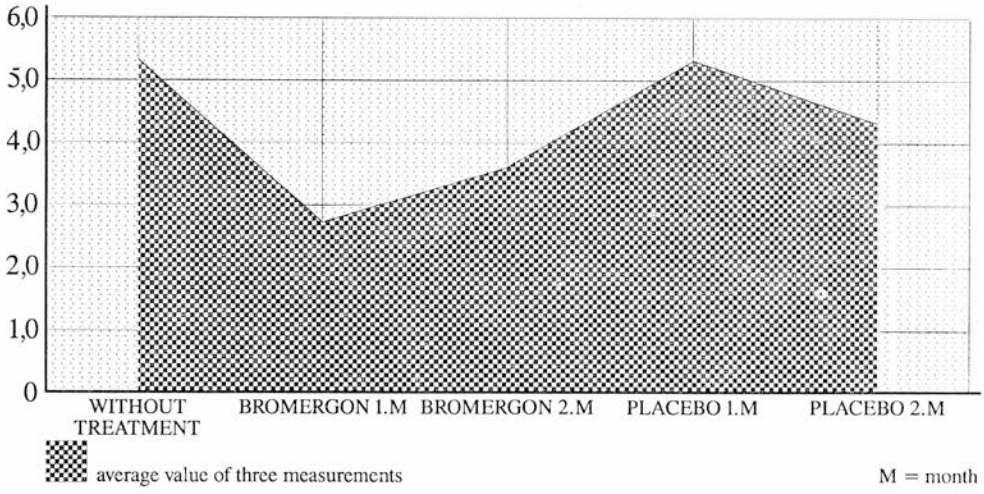

Fig. 5. — Mastodynia, assessed by linear analog scale one week before onset of menstruation.

DISCUSSION

Since the clinical picture of PMS is varied and its etiology still obscure, numerous treatments have been proposed. Thus the use of progesterone in the management of PMS is based on the notion of a hormonal imbalance between estrogen and progesterone and progesterone deficiency in the luteal phase of the menstrual cycle as causative factors in the development of the premenstrual syndrome. However, controlled double-blind studies failed to demonstrate any improvement in PMS symptoms during progesterone therapy ([4]).

Similarly, thyrotoxine, the use of which is based on the hypothesis that a thyroid dysfunction might be involved in the genesis of PMS, proved effective in one study only ([5]), while other detailed analyses failed to demonstrate any differences in either basal or TRH-stimulated thyroid hormone levels between patients with PMS and healthy controls ([6]).

Excess prostaglandin production has also been proposed as a possible etiologic agent, resulting in the use of prostaglandin synthesis inhibitors in the management of PMS ([7, 8]). Double-blind placebo-controlled studies confirmed the efficacy of prostaglandin inhibitors in relieving PMS symptoms ([9, 10]), especially in dysmenorrheic women. However, their adverse effects are very unpleasant, including possible hemato-, nephro- or neurotoxic effects.

Another agent frequently used in the management of PMS is pyridoxine (vitamin B_6), a significant cofactor for enzymes involved in the synthesis of dopamine, serotonin and certain prostaglandins ([1]). Since dopamine and serotonin are known for their mood-modifying effects, it was anticipated that the use of pyridoxine would reverse the neurotransmitter imbalance in PMS. However, the initial enthusiasm about the use of pyridoxine waned with further research which failed to demonstrate the superiority of pyridoxine over placebo ([11, 12]).

More recent studies demonstrated the beneficial effects of danazol on PMS symptoms ([13, 14]). However, since low-dose danazol does not inhibit the ovulation, pregnancy is not recommended because of the drug's teratogenic potential. This, to-

gether with its known adverse effects, considerably limit the therapeutic usefulness of danazol in the management of PMS.

A double-blind placebo-controlled study demonstrated the efficacy of hypothalamic gonadotropin-releasing factor analogs in the treatment of PMS ([15]). However, this is an extreme therapeutic approach since it causes complete cessation of ovarian function and pituitary desensibilization with all their consequences.

The use of bromocryptine in the treatment of PMS has several justifications. It produces a direct effect on the breast and is therefore responsible for symptoms such as congestion, tenderness and pain. Prolactin secretion increases in response to stress and promotes water, potassium and natrium retention.

Although the effect of bromocryptine on PMS symptoms has been extensively documented in numerous studies, there is still no consensus of opinion on its place in therapy. Thus, some studies confirmed the beneficial effects of bromocryptine on the PMS symptoms ([16, 17]), while others, mainly those using lower doses (2.5 mg daily), failed to demonstrate any therapeutic effect ([18]).

From the observation that body weight significantly decreased during Bromergon therapy, it could be concluded that in patients with PMS prolactin tends to increase water and sodium retention despite normal concentrations. Likewise, the significant reduction in abdominal tension and edema observed during Bromergon therapy in comparison with the treatment-free and placebo periods could be accounted for by a similar mechanism of action. The linear analog scale also demonstrated a significant improvement in breast tenderness during Bromergon therapy. These findings are concordant with previous reports of the efficacy of Bromergon in relieving premenstrual mastodynia.

The results of this study have demonstrated che efficacy of Bromergon in the management of PMS in comparison with other currently used medications. It acts polysymptomatically, affecting mainly symptoms referable to fluid retention (i.e. body weight, abdominal tension, breast tenderness, edema), its effect on psychic symptoms being somewhat less pronounced.

Absence of adverse reactions and lack of effect on blood tests, electrolytes and transaminases are another advantage over other medications currently used in the management of premenstrual syndrome.

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