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Myo-Inositol has no Beneficial Effect on Premenstrual Dysphoric Disorder

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Summary

Inositol, a simple isomer of glucose, which serves as a precursor in the phosphatidyl-inositol (PI) second messenger cycle, was shown to be effective in double-blind, placebo-controlled studies of depression, panic and obsessive compulsive disorders as well as in bulimia. The following study was designed to investigate whether inositol has beneficial effects in another disorder shown to be responsive to SSRIs: premenstrual dysphoric disorder (PMDD).

Eleven female patients with PMDD diagnosed according to DSM-IV participated in a cross-over, double-blind, placebo-controlled trial. The active drug was myo-inositol, 12 g daily, whereas placebo was d-glucose administered at the same dose. Each drug was given during the luteal phase only (14 days prior to menses). For each patient treatment alternated between these two drugs for six menstrual cycles. No beneficial effect was demonstrated for inositol over placebo.

Key words: *myo-inositol, premenstrual dysphoric disorder.*

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Introduction

Premenstrual dysphoric disorder (PMDD) is a subcategory of premenstrual syndrome (PMS); it is characterized mainly by tension, irritability and dysphoria and affects 3 - 8 % of women in their reproductive years (Johanson et al 1988; Steiner et al 1995). Steiner et al (1995) found a beneficial effect of fluoxetine 20 and 60 mg daily, given continuously for six consecutive menstrual cycles, in a large group of women with PMDD. Fluoxetine given at 20 mg daily was as effective as 60 mg daily with fewer side effects. However, this compound may cause anorgasmia, nausea, diarrhoea and have other side effects, and clearly more benign treatments are desirable.

Inositol, a simple isomer of glucose, serves as a precursor in the phosphatidyl-inositol (PI) second messenger cycle (Berridge et al 1982). Treatment with 12 g inositol per day causes a 70 % increase of cerebrospinal (CSF) levels (Levine et al 1993). Inositol was shown to be effective in double-blind, placebo-controlled studies of depression as well as in panic and obsessive compulsive disorders (Levine et al 1995; Benjamin et al 1995; Fux et al 1996) (three psychiatric disorders possibly involving the serotonergic systems). We also found inositol to be effective in bulimia (Gelber et al 2001). All these disorders also respond to serotonin selective reuptake inhibitors (SSRI) such as fluoxetine. The following study was designed to investigate whether inositol has beneficial effects in another disorder shown to be responsive to SSRIs: premenstrual dysphoric disorder (PMDD) (Steiner et al 1995).

The results from randomized, placebo-controlled trials in women with PMDD have demonstrated that luteal phase SSRI administration may offer an attractive intermittent treatment option for this intermittent disorder (Young et al 1998; Wikander et al 1998). Steiner and Born (2000), in a review of the literature, claimed that the onset of response with SSRIs in PMDD is very rapid and can sometimes be as short as one to two days. Based upon this last observation we decided to use in this study a design of alternated treatment between inositol and placebo.

Methods

• Patients

Premenstrual dysphoric disorder was diagnosed according to modified DSM-IV criteria. Thus

patients had to have at least five of 11 listed symptoms of category A, with one of the symptoms being Symptom 1, 2, 3 or 4. No daily ratings were performed for subjects for two consecutive cycles prior to the study. So, at entry to the study, the subjects had a provisional diagnosis of PMDD. However, at each successive visit throughout the study the diagnosis was confirmed by an experienced psychiatrist according to the subject's report, and notes were taken between visits. Also the visual scales (see below) were used throughout the study to further confirm cyclicity. Both at baseline and for two consecutive months after the study significant interference with social or role functioning was verified with each patient.

Twelve female outpatients were recruited into the study. One woman, aged 38, dropped out of the study at the second visit due to lack of cooperation. Demographic characteristics for the eleven patients participating in the study were as follows: mean age ± SD was 35.9 ± 5 years (range: 30-43); eight women were married, two single and one divorced; mean number of pregnancies ± SD was 1.6 ± 1 (range: 0-3); mean number of children ± SD was 1.5 ± 1 (range: 0-3); mean duration of illness ± SD was 6.5 ± 4 years (range: 2-15 years); mean duration of menstrual cycle ± SD was 28.5 ± 0.8 days; mean duration of symptoms within a given menstrual cycle ± SD was 9.1 ± 3 days. All women were in good physical health and had no history of any other neurological, psychiatric, gynaecological or endocrinological disorder. All women had regular menstrual cycles and none of them was pregnant or using oral contraceptives at the time of the study. To avoid including women with anovulatory cycles, only women with menstrual cycles of 24-35 days duration were recruited. None of them had alcohol or drug abuse. All participants gave informed consent after full disclosure of the study aims and risks.

• Measurement

Ten rating scales were used in the study, as follows:

1,2,3: Three analogue scales for psychic symptoms: tension, irritability and dysphoria.

4,5,6: Three analogue scales for physical symptoms: headache, bloating and breast tenderness.
(These visual analogue scales were found to be effective tools for measuring changes over time in response to drug therapy, and their reliability and validity has been documented (McCormak et al 1998). They are 100 mm scales in which 0 mm represents no symptoms and 100 mm represents extreme symptoms.)

7: Hamilton Depression Rating Scale (HDRS).

8: Clinical Global Impression (CGI) - severity scale.

9: Self-rating scale for premenstrual tension syndrome (PMTS) (Steiner et al 1980) of 36 items scale covering premenstrual symptoms for a particular day. The total score can range from 0, indicating no symptoms, to 36, indicating all symptoms are present and severe.

10: Observer-rating scale of 10 items (Steiner et al 1980).

• Study design

Patients were randomized to start the study with either inositol or placebo. The study was conducted for six consecutive menstrual cycles. Treatment was administered during the luteal phase only (14 days before the expected menses). Subjects starting with inositol were treated with this drug in the first, third and fifth menstrual cycles while receiving placebo in the second, fourth and sixth menstrual cycles. For patients starting with placebo the order of treatment was vice versa. The study included 13 visits, one at baseline and two during each menstrual cycle, one of which was during the follicular phase and the other during the late luteal phase. All scales were rated at each visit, either by the examiner or the patient.

Results

Inositol was not found to be superior to placebo in this study in any of the scales used (Table 1). Side effects were few and included mild and transient bloating in two patients on inositol and no complaints on placebo.

Table 1

Effects of inositol and placebo on the study scales*

	Scale	Baseline	Mean Placebo Change	Mean Inositol Change	Statistical Significance
1	Tension Analogue Scale	60 ± 15	27.5 ± 16	30.3 ± 20	NS
2	Irritability Analogue	65.5 ± 14	32.4 ± 16	27.5 ± 18	NS
3	Sadness Analogue	64.5 ± 17	27.5 ± 21	28.4 ± 20	NS
4	Headache Analogue	40.1 ± 28	16.0 ± 12	23.0 ± 15	NS
5	Bloating Analogue	45.5 ± 25	25.7 ± 19	24.8 ± 22	NS
6	Breast Tenderness	44.5 ± 22	29.7 ± 23	25.7 ± 23	NS
7	HDRS	8.6 ± 6	2.7 ± 3	4.3 ± 3	NS
8	CGI Severity	2.5 ± 0.7	1.1 ± 0.7	1.2 ± 0.8	NS
9	Self-rating for PMTS	26.4 ± 7	12.3 ± 7	14.9 ± 6	NS
10	Observer-rating, PMTS	17.8 ± 6	8.4 ± 5	10.2 ± 5	NS

* Change scores are mean values of pre- minus post-treatment of three alternate months of treatment with a given study drug (inositol or placebo).

Discussion

This study was designed on the premise that inositol's mechanism of action involves serotonergic systems, as inositol was found to be effective in double-blind studies in major depression, panic disorder, obsessive-compulsive disorder

and bulimia (Levine et al 1995; Benjamin et al 1995; Fux et al 1996; Gelber et al 2001; Einat et al 2001), much like the SSRIs. Contrary to our hypothesis, the study suggests that inositol has no beneficial effect in PMDD and thus this result may not be consistent with the previous cumulative data supporting a serotonergic mode of action for inositol in psychiatric disorders. On the other hand, it may be conceived that the serotonergic mechanisms underlying PMDD are different from those underlying major depression as the clinically relevant beneficial effects of serotonergic agents such as fluoxetine and clomipramine occur faster in PMDD than in major depression. There is now data available which demonstrates that inositol seems to affect serotoninergic systems associated with 5-HT_2 receptors. Einat et al (2001), who drew a psychopharmacological profile of inositol's behavioural effects by exploring the interactions between the drug and specific receptor agonists and antagonists in the forced swim test, concluded that 5-HT_2 receptors seem to mediate the antidepressant effect of inositol. This may indicate that 5-HT_2 receptors may not be involved in the mechanism of PMDD. On the other hand, m-CPP, an agent with a moderately high affinity for a number of 5-HT receptors (particularly 5-HT_{2A}, 5-HT_{2B}, 5-HT_3 and 5-HT_{1B}) (Murphy et al 1991; Hoyer and Schoeffter 1991) was shown in a well-designed, controlled study to improve dysphoria in women suffering from PMS (Su et al 1997). These effects of m-CPP may be mediated via 5-HT_2 receptors or via other types of 5-HT receptors, leaving open the question of the role of 5-HT_2 receptors in the treatment of PMDD. Finally, another possibility is that our subjects showed a floor effect since both placebo and inositol led to a marked improvement.

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References

Benjamin J, Levine J, Fux M, Aviv A, Levy D, Belmaker RH (1995) Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. Am J Psychiatry 152: 1084-1086.

Berridge MJ, Downes CP, Hanley MR (1982) Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem J 206: 587-595.

Einat H, Clenet F, Shaldubina A, Belmaker RH, Bourin M (2001) The antidepressant activity of inositol in the forced swim test involves 5-HT(2) receptors. Behav Brain Res 118: 77-83.

Fux M, Levine J, Aviv A, Belmaker RH (1996) Inositol treatment of obsessive-compulsive disorder. Am J Psychiatry 153: 1219-1221.

Gelber D, Levine J, Belmaker RH (2001) Effect of inositol on bulimia nervosa and binge eating. Int J Eat Disord 29: 345-348.

Hoyer D, Schoeffter P (1991) 5-HT receptors: subtypes and second messengers. J Recept Res 11: 197-214.

Johanson SR, McChesney C, Bean JA (1988) Epidemiology of premenstrual symptoms in a nonclinical sample: prevalence, natural history and help seeking behavior. Journal of Reproductive Medicine 33: 340-346.

Levine J, Rapaport A, Lev L, Bersudsky Y, Kofman O, Belmaker RH, Shapiro J, Agam G (1993) Inositol treatment raises CSF inositol levels. Brain Res 627: 168-170.

Levine J, Barak Y, Gonzalves M, Szor H, Elizur A, Kofman O, Belmaker RH (1995) Double-blind, controlled trial of inositol treatment of depression. Am J Psychiatry 152: 792-794.

McCormak HM, Horne DJ, Sheather S (1998) Clinical applications of visual analogue scales: a critical review. Psychol Med 18: 1007-1019.

Murphy DL, Lesch KP, Aulakh CS, Pigott TA. (1991) Serotonin-selective arylpiperazines with neuroendocrine, behavioral, temperature, and cardiovascular effects in humans. Pharmacol Rev 43: 527-552.

Steiner M, Born L (2000) Diagnosis and treatment of premenstrual dysphoric disorder: an update. Int Clin Psychopharmacol 15 (Suppl 3): S5-S17.

Steiner M, Haskett RF, Carroll BJ (1980) Premenstrual tension syndrome: the development of research diagnostic criteria and new rating scales. Acta Psychiat Scand 62: 177-190.

Steiner M, Steinberg S, Stewart D, Carter D, Berger C, Reid R, Grover D, Streiner D (1995) Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med 332: 1529-1534.

Su TP, Schmidt PJ, Danaceau M, Murphy DL, Rubinow DR (1997) Effect of menstrual cycle phase on neuroendocrine and behavioral responses to the serotonin agonist m-chlorophenylpiperazine in women with premenstrual syndrome and controls. J Clin Endocrinol Metab 82: 1220-1228.

Wikander I, Sundblad C, Andersch B, Dagnell I, Zylberstein D, Bengtsson F, Eriksson E (1998) Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 18: 390-398.

Young SA, Hurt PH, Benedek DM, Howard RS (1998) Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 59: 76-80.