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Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study

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Abstract

In a double-blind, placebo controlled study, conjugated estrogens (CE) (0.625 mg/day) were added to a fixed dosage of haloperidol (5 mg daily). Forty-four female inpatients with acute schizophrenia were included in the study and randomized to one of the groups; 40 patients completed the trial. They were followed for 28 days and evaluated periodically with the BPRS, Negative Symptoms Rating Scale, Simpson Angus Extrapyramidal Rating Scale and UKU rating scale. Hormonal concentrations (estradiol, estrone, progesterone, FSH, LH and prolactine) were measured at baseline and weekly throughout the trial. Both groups showed similar clinical improvement during the evaluation, although there was a trend for the CE group to show a better improvement than the placebo group ($p < 0.10$). Side effects and the use of anticholinergics were similar in both groups. Conjugated estrogens caused elevation only of estrone levels in the CE group; estradiol and prolactin showed a similar profile for both groups. Our negative findings regarding the antipsychotic effect of conjugated estrogens does not preclude, however, a possible efficacy of other estrogens, such as 17-beta-estradiol, in schizophrenia.

Keywords: Schizophrenia; Women; Gender; Conjugated estrogens; Treatment; Antipsychotics

1. Introduction

Compelling evidence suggests that there are gender differences in schizophrenia regarding age at onset of the disease, premorbid functioning, course, prognosis, treatment response, among others, favoring female patients (for reviews, see Leung and Chue 2000; Castle et al., 2000; Grigoriadis and Seeman, 2002). One of the possible explanations for these differences is a protective effect of estrogens (Riecher-Rössler and Häfner, 1993); some studies have shown that estrogen levels may influence the symptomatology (Riecher-Rössler et al., 1994) and treatment response in schizophrenia (Gattaz et al., 1994). Additionally, it was found that estrogens modulate dopaminergic D2 receptors and have a antipsychotic-like effect, probably augmenting the efficacy of antipsychotic medications (Häfner et al., 1991; Cyr et al., 2002).

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The therapeutic use of estrogens added to antipsychotic drugs in the treatment of schizophrenic patients has been investigated in a few trials. Kulkarni et al. (1996) studied the effect of estradiol in schizophrenic women in an open-label trial. Eleven women with acute psychosis received 0.02 mg estradiol added to antipsychotic treatment for 8 weeks, and their treatment response was compared to seven women with similar symptoms receiving only antipsychotic treatment. The group that received estradiol plus antipsychotics showed a more rapid improvement in the psychotic symptoms, but this difference was not sustained for the whole trial. By the 8th week, both groups showed similar improvement in psychopathology.

A double-blind, 4-week study was performed by Kulkarni et al. (2001), comparing three groups of women ($n = 12$, in each group) that received standardized antipsychotic treatment plus 50 μg transdermal estradiol or 100 μg transdermal estradiol or transdermal placebo. The 50 μg estradiol group improved more than the placebo group but women who received 100 μg estradiol had a even greater improvement than the 50 μg estradiol and the placebo groups.

Conjugated estrogens (CE) are commonly used as hormonal replacement and are well tolerated. In the present study, we investigated whether an estradiol-independent hormonal replacement would also augment the antipsychotic effect of haloperidol. For this purpose, we performed in 40 schizophrenic women a placebo-controlled double-blind trial with conjugated estrogens, which contain mainly estrone and only minimal concentrations of estradiol, added to a fixed daily dose of haloperidol (5 mg) for 4 weeks.

2. Methods

The study was approved by the local ethical committee and followed the recommendations of the Declaration of Helsinki. Forty-four inpatient women of child-bearing age with acute schizophrenia were recruited. All patients gave their written informed consent to participate the study. Patients were admitted during the active phase of illness and met DSM-IV criteria for schizophrenia. They had a minimum total score of 18 points in the Brief Psychiatric Rating Scale (18 items, 0 = not present to 6 = extremely severe)(Overall and Gorham, 1962). All women were submitted to a gynecological evaluation to exclude estrogen-dependent diseases; two women were excluded due to the presence of fibroids. Forty-two women were included in the study. Of these patients, there were two dropouts. One patient refused to take oral medication and the other showed a worsening of the symptoms and was excluded. The final sample included 40 patients that completed the study. They were 32.3 ± 8.2 years of age (range 18–49 years). Twenty-one patients were randomized to the conjugated estrogens group and 19 to placebo. Their demographic characteristics are summarized on Table 1.

After a washout period of at least 3 days, on baseline (day 0) patients were randomized to receive a fixed dose of haloperidol (5 mg/day PO) plus either placebo or a fixed dose of 0.625 mg/day PO of conjugated estrogens for 4 weeks. Efficacy was evaluated by the Brief Psychiatric Rating Scale (BPRS) total score, the BPRS positive score (including the following items: unusual thought content, hallucinatory behavior and suspiciousness) and the Negative Symptoms Rating Scale (Iager et al., 1985). The side effects were evaluated by the Extrapyramidal Symptoms Rating Scale (Simpson and Angus, 1970) and UKU Side Effects Rating Scale (Lingjaerde et al., 1987) at baseline and days 3, 7, 14, 21 and 28. Anticholinergics (biperiden, up to 6 mg/day PO) and benzodiazepines (diazepam up 40 mg/day PO) were allowed in case of extrapyramidal symptoms and agitation or insomnia, respectively.

Table 1
Demographic characteristics of the sample (mean ± S.D.)

	Conjugated estrogens ($n = 21$)	Placebo ($n = 19$)	p
Age (years)	34.1 ± 7.9	30.4 ± 8.3	0.116
Age at first onset (years)	26.4 ± 8.9	22.8 ± 6.3	0.225
Age at first hospitalization (years)	31.2 ± 7.6	24.5 ± 6.3	0.002
Number of previous hospitalizations	5.0 ± 6.3	4.3 ± 3.1	0.227

Blood samples were also collected on baseline and days 7, 14, 21 and 28 to measure serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol, estrone and progesterone. Separate fluorimetric assays (Delfia, PerkinElmer, Wallac Oy, Turku, Finland) were performed on each individual sample for all hormonal assays except for estrone, which was measured by radioimmunoassay (Diagnostics Laboratories DSL, Texas, USA).

Statistics was performed with SPSS version 10. Repeated measures MANOVA was used to evaluate the differences between groups (CE versus placebo) along the study. Additionally, due to the skewness of the psychopathological data, nonparametric tests (Mann–Withney) were used to compare means at the different time points. Calculation of BPRS changes were based on percents of baseline values to correct for differences at baseline. Chi-square was used to analyze the differences between groups in the case of categorical variables, such as of demographic data and the use of antiparkinsonians.

3. Results

The repeated measures MANOVA showed no statistically significant differences between groups (CE versus placebo) along the study. Both groups showed a significant ($p < 0.001$) improvement of symptoms. As age at first hospitalization was different between groups, this variable was introduced as covariable, but this did not change the results obtained.

Both the Conjugated Estrogens group and the Placebo group showed a similar improvement on the BPRS total score along the study. There was only a trend towards a better response on days 3 ($p = 0.052$), 21 ($p = 0.065$) and 28 ($p = 0.078$) for the CE group (Fig. 1).

Considering only the BPRS positive symptoms, the CE group showed a trend towards a better improvement on day 28 ($p = 0.065$). There was no difference between both groups in relation to the improvement of negative symptoms, as measured by the NSRS. Rates of improvement for the total BPRS, the BPRS-positive symptoms score and the NSRS were also calculated and for each evaluation day in relation to

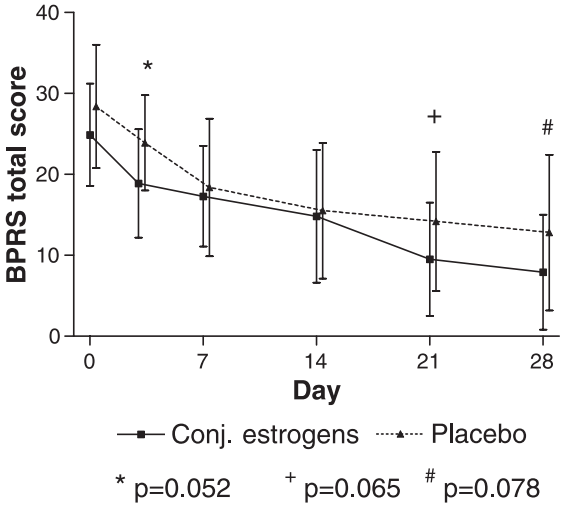

Fig. 1. Clinical improvement as measured by the BPRS total score (mean ± S.D.) for the conjugated estrogens and the placebo groups.

baseline. No significant differences were observed for these variables between CE and placebo groups along the study.

EPS scores were significantly higher for the CE group only day 21 ($p = 0.02$). On the remaining evaluation visits, there were no differences on EPS scores between the two groups. Other side effects (as measured by the UKU scale) were less frequent on the CE group, reaching significance on baseline ($p = 0.02$) and day 28 ($p = 0.009$). There were no significant differences between the groups in the proportion of patients as well in the daily doses of anticholinergic drugs.

Serum concentrations of estradiol were higher for the CE group along the study, but the differences did not reach significance. Serum concentrations of estrone were significantly higher ($p < 0.001$) for the CE group along the 4 weeks of the study. There was no difference on serum concentrations of progesterone along the study for both groups of patients. As expected, prolactin levels increased similarly in both groups along the study due to the effect of haloperidol. There was a large variability of FSH and LH serum concentrations for both groups along the study but no significant differences between CE and placebo groups were observed. We did not observe any significant correlation between the severity of symptoms

and the hormonal concentrations in serum. The hormonal values are available from the authors upon request.

4. Discussion

Both groups of patients showed similar improvement in general psychopathology, positive and negative symptoms. Although there was a trend for the CE group to a better improvement than the placebo group, the difference did not reach statistical significance in the 28-day period of the study. It cannot be ruled out that in a study with a longer duration, a significant effect size could be obtained, although Kulkarni et al. (1996) observed differences in the treatment with estradiol only during the first 15 days of treatment. The unspecific effect of CE was not strong enough to produce a better improvement of the patients as it occurred in other studies when 17-beta-estradiol was used (Kulkarni et al., 1996, 2001).

There was also no difference between the two groups in terms of extrapyramidal side effects. Both groups showed a very low degree of side effects, probably due to the small doses of haloperidol (5 mg/day) used during the trial. It is of interest that patients on CE showed slightly but significantly more EPS on day 21. It is tempting to speculate that this difference results from the discrete increment of estradiol in this group, which would act a dopaminergic blockade in striatum and consequently more EPS.

An increase of estrone levels was observed along the study in the CE group, due to the use of conjugated estrogens, instead of pure beta-estradiol. The serum level of estradiol did not change significantly along the study. As expected, prolactin levels increased in both groups.

It cannot be ruled out that an eventual clinical efficacy of CE was overshadowed by a more expressive effect of haloperidol. However, even if present, we judge that, clinically, the effect of CE would not be relevant enough to justify further trials in schizophrenia. Conversely, long-term studies with 17-beta-estradiol are warranted, for instance, to investigate a possible efficacy in the prevention of psychotic relapse in schizophrenic women, who have a trend to relapse in the pre-menstruum.

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