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Short communication

A randomized pilot trial of estrogen replacement therapy in post-menopausal women with Parkinson's disease☆,☆☆,★,★★

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ABSTRACT

Objective: To assess short-term safety and tolerability of estrogen replacement therapy in post-menopausal women with Parkinson's disease (PD).
Methods: In a multi-center randomized, double-blind, placebo-controlled pilot trial, post-menopausal women with PD and motor fluctuations received either 0.625 mg/day of conjugated equine estrogens or matching placebo for 8 weeks. The primary outcome was the ability of participants to complete the trial. Other outcome measures included adverse events and changes from baseline to Week 8 in Unified PD Rating Scale scores, "on" time, dyskinesia ratings, and neuropsychological test results.
Results: Twenty-three women (age 62.9(6.3) years, total Unified PD Rating 25.0(13.4), 8.8(6.0) years since symptom onset) were enrolled. There were no serious adverse events. One subject withdrew due to worsening of tremor and dystonia. The most commonly reported adverse events were vaginal spotting, breast enlargement and breast tenderness. The estrogen group showed improved total and motor Unified PD Rating scores although these did not reach statistical significance (mean changes from baseline, estrogen vs. placebo: Total −5.0 vs. 2.8, treatment effect = −7.8, $p = 0.10$; Motor −3.0 vs. 2.4, treatment effect = −5.4, $p = 0.16$).
Conclusions: Estrogen replacement therapy was safe and well-tolerated over 8 weeks in post-menopausal women with advanced PD. This pilot data suggests that estrogen replacement may be associated with improvement in motor symptoms. While larger studies of longer duration are necessary to determine the effects of estrogen in PD, the complex risk/benefit profile and continued controversy surrounding estrogen are obstacles to clinical trials.

1. Introduction

Evidence from basic science, epidemiology and clinical research suggests that estrogens may influence the onset and severity of Parkinson's disease (PD). Animal studies show estrogenic modulation of pre- and post-synaptic indices of dopaminergic function [1] and evidence of estrogen's ability to protect dopaminergic neurons. Clinical studies show that women with PD are less likely to have used estrogen replacement therapy (ERT) and more likely to have had surgical oopherectomy [2]. Gender differences are documented in the efficacy, tolerability and pharmacokinetics of antiparkinsonian medications [3] and ERT was shown to improve motor symptoms and reduce "off" time in patients with motor fluctuations [4]. Most women developing PD are post-menopausal. Therefore, better understanding of the effects of ERT in post-menopausal women with PD is important for clinical management.

We conducted a preliminary controlled trial to examine the short-term safety and tolerability of ERT in post-menopausal women with PD. Secondary aims included the assessment of the effects of ERT on primary motor symptoms, motor fluctuations and cognitive/behavioral functions.

2. Methods

The **POETRY** trial (**P**arkinson's Disease **o**n **Est**rogen **R**eplacement in the Menopause **Y**ears) was a multi-center, randomized, double-blind, placebo-controlled, parallel group study to examine the safety and tolerability of conjugated equine

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★ The Parkinson Study Group maintained the database and carried out independent analysis of the data.
★★ This study was presented in abstract form and as a platform presentation on October 8, 2006 at the 20th Annual Symposia on Etiology, Pathogenesis and Treatment of Parkinson's Disease and Other Movement Disorders.

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estrogens (CEE) in post-menopausal women with PD experiencing motor fluctuations. Participating subjects were randomized to CEE or matching placebo in a 2:1 ratio and followed for 2 months. The primary outcome measures for safety and tolerability were occurrences of adverse events and the ability of the participant to complete the trial. Exploratory outcome measures of efficacy included the United Parkinson's Disease Rating Scale (UPDRS), patient-completed diaries of motor fluctuations, and an extensive neuropsychological test battery. The protocol and consent documents were approved by institutional review boards at all 6 participating sites, and all subjects gave informed consent for participation.

Subjects were primarily recruited from each research site's clinic population. Eligible patients included women with at least three of the four cardinal signs of PD, Hoehn and Yahr (HY) stage of I to III "on" and maximum of IV "off", motor fluctuations averaging at least 2 h daily "off", stable dosages of antiparkinsonian and antidepressant medications, Mini Mental State Examination score >24, laboratory confirmation of menopause and gynecological clearance (negative pap smear, mammogram, breast and pelvic exams within 12 months).

Potential subjects were excluded if they had atypical parkinsonism, presence of severe dyskinesia, age >75 years, use of ERT within 6 months, use of tamoxifen, raloxifene, tacrine, donepezil, rivastigmine, galantamine or memantine, a history of thromboembolic disorder, myocardial infarction, angina, stroke, transient ischemic attack, hypercoagulable state, abnormal vaginal bleeding, cancer of the breast or uterus, unstable medical or psychiatric disorders within 6 months. Diary training was performed, followed by simultaneous diary completion by the participant and the coordinator, with 75% concordance required for enrollment.

At the baseline visit, participants were randomized to 0.625 mg CEE or matching placebo in a 2:1 (ERT:placebo) ratio. The active medication and matching placebo were supplied by Wyeth Pharmaceuticals. Although this study population included both hysterectomized and nonhysterectomized women, the brief duration of ERT in this study was not sufficient to result in clinically significant endometrial hyperplasia and did not necessitate the addition of a progestin.

Baseline assessments included a medical/gynecological history, general physical and neurologic exams, UPDRS, Schwab and England Activities of Daily Living (S/E ADL) Scale, the Lang-Fahn Dyskinesia/ADL Scale and a neuropsychological test battery conducted while "on". The battery of 16 tests was chosen for applicability to domains influenced by PD and estrogen in previous studies. Subjects were re-evaluated at 1 month and 2 months following randomization. Diaries were completed for 3 consecutive days prior to all visits, classifying each 30-min period as "on without dyskinesia", "on with dyskinesia", "off", or "asleep". The UPDRS and Lang-Fahn Dyskinesia/ADL scale were administered at each visit. The S/E ADL scale, neuropsychological battery and the Clinical Neuropsychological Impression of Change (a blinded, consensus arbitration by two neuropsychologists based on each subject's baseline and final neuropsychological test performance) were assessed at Month 2.

Safety was assessed at each visit by screening for adverse events, deep vein thrombosis, and a menopausal symptom checklist. Compliance with study medication was assessed using pill counts, and serum estradiol levels were obtained at screening and Month 2. The investigator, coordinator and participant were asked to guess the treatment assignment at the 2-month visit. A Safety Monitoring Committee composed of three members (gynecologist, neurologist and statistician) reviewed all safety data in an unblinded fashion after groups of 10 subjects completed the 2-month visit. The predetermined stopping guideline was termination if any of the following occurred 3 times in the ERT group: stroke, myocardial infarction, deep vein thrombosis or pulmonary embolus.

2.1. Statistical analysis

Analyses of the neuropsychological test results involved fitting an analysis of covariance model with change from baseline to Month 2 in the variable of interest as the dependent variable, treatment group as the factor of interest, and the baseline value of the outcome variable as a covariate. The significance of the differences in adjusted mean response between the ERT and placebo groups was assessed using this model. Ninety-five percent confidence intervals for the differences in the adjusted group means were likewise computed using this model. A significance level of 5% (two-tailed) was used for all tests.

Similar analyses were performed for changes in UPDRS scores, S/E ADL, Lang-Fahn Dyskinesia/ADL Scale, and percent "on" time per day. Other outcomes, including safety and tolerability outcomes, are summarized descriptively.

3. Results

Twenty-three post-menopausal women with PD were enrolled between October, 2003 and March, 2006 at 6 participating sites (see Appendix). Study recruitment was much slower than anticipated; enrollment was planned for 12 months but the study was stopped after 28 months due to expiration of the study drug and inability to obtain new drug supply with matching placebo.

Baseline characteristics of the two treatment groups are shown in Table 1. The ERT group was, on average, somewhat younger (61.6(6.1) vs. 65.4(6.2) years) and had less time since symptom onset (7.9(6.4) vs. 10.6(5.0) years). Nevertheless, the mean total UPDRS was somewhat higher in the ERT group (26.8(15.2) vs. 21.7(8.7)).

Twenty-two of 23 subjects completed the trial. A single subject in the ERT group withdrew citing worsened tremor and dystonia. The investigator did not observe any change. No subjects required adjustment of antiparkinsonian medications. There were no notable changes in vital signs and no serious adverse events reported. Seventy-three percent (11/15) in the ERT group and 38% (3/8) in the placebo group reported at least one adverse event. The most commonly reported adverse events were vaginal spotting and breast enlargement (3 subjects each) and breast tenderness (2 subjects). All reports of spotting and breast tenderness and 2 of 3 reports of breast enlargement were in the ERT group.

Efficacy outcomes are shown in Table 2. Although the sample size was small, there were trends toward ERT-associated improvement in the total UPDRS (treatment effect −7.8 points, 95% confidence interval [CI] −17.4 to 1.7, $p = 0.10$) and the UPDRS motor subscale (treatment effect −5.4 points, 95% CI -13.0 to 2.3, $p = 0.16$). A similar trend was noted for the S/E ADL "on" rating ($p = 0.14$, Table 2). No differences between ERT and placebo groups were detected for the mental and ADL UPDRS subscales, diary outcomes, and the Lang-Fahn Dyskinesia/ADL Scale. No differences were apparent on the 16 measures in the neuropsychological battery (on-line Supplementary Material). For the Clinical Neuropsychological Impression of Change, 64% of the ERT-treated subjects were judged to be "unchanged" (7% "worse" and 29% "better"), while 63% of the placebo-treated subjects were judged to be "better" (13% "worse" and 25% "unchanged").

Mean compliance with study medication was 88% with ERT and 92% with placebo. Laboratory testing confirmed that all subjects had undetectable (<35 ng/ml) serum estradiol at baseline. At Month 2, 12 of 15 subjects in the ERT group had detectable estradiol levels (mean = 81.8(37.6) ng/ml, range 38–150) and 7 of 8 subjects in the placebo group had undetectable levels (one had a level of 69 ng/ml). No association was found between serum estradiol level and change in total or motor UPDRS.

Table 1
Baseline demographic and clinical characteristics by treatment assignment.

Variable	Placebo ($n = 8$)	ERT ($n = 15$)
Age	65.4 (6.2)	61.6 (6.1)
Caucasian (%)	100%	100%
Years of education	13.6 (1.7)	14.3 (2.8)
Years since PD onset	10.6 (5.0)	7.9 (6.4)
Years since diagnosis	8.4 (4.3)	6.4 (6.8)
Years since menopause onset	14.4 (7.4)	11.2 (7.4)
Levodopa dosage (mg/day)	696.4 (213.3)	526.7 (295.9)
% "On" time	68.9 (10.6)	70.9 (10.8)
% "On" time w/o dyskinesia	62.7 (16.5)	60.0 (12.1)
% Asleep time	29.6 (6.6)	31.2 (7.3)
H/Y Stage (%)		
2.0	12.5%	26.7%
2.5	25.0%	26.7%
3.0	62.5%	46.7%
UPDRS		
Mental	2.0 (1.2)	1.8 (1.6)
ADL	5.8 (3.4)	6.5 (5.3)
Motor	13.9 (7.3)	18.5 (11.6)
Total	21.7 (8.7)	26.8 (15.2)
S/E ADL "On"	87.5 (6.0)	90.7 (4.6)
S/E ADL "Off"	70.6 (7.8)	75.3 (15.6)

Values are mean (standard deviation) unless otherwise indicated.
UPDRS = Unified Parkinson's Disease Rating Scale.
H/Y = Hoehn and Yahr Staging.
S/E ADL = Schwab and England Activities of Daily Living Scale.