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Hormone Replacement Therapy in Women with Epilepsy: A Randomized, Double-Blind, Placebo-Controlled Study

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Summary: *Purpose:* Previous reports have suggested that hormone replacement therapy (HRT) could increase seizure activity in women with epilepsy. We sought to determine whether adding HRT to the medication regimen of postmenopausal women with epilepsy was associated with an increase in seizure frequency.

Methods: This was a randomized, double-blind, placebo-controlled trial of the effect of HRT on seizure frequency in postmenopausal women with epilepsy, taking stable doses of antiepileptic drugs (AEDs), and within 10 years of their last menses. After a 3-month prospective baseline, subjects were randomized to placebo, Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or CEE/MPA) daily, or double-dose CEE/MPA daily for a 3-month treatment period.

Results: Twenty-one subjects were randomized after completing baseline. The subjects' ages ranged from 45 to 62 years (mean, 53 years; SD, ±5), and the number of AEDs used ranged from none to three (median, one). Five (71%) of seven subjects taking double-dose CEE/MPA had a worsening seizure frequency of at least one seizure type, compared with four (50%) of eight taking single-dose CEE/MPA and one (17%) of six taking placebo ($p = 0.05$). An increase in seizure frequency of the subject's most severe seizure type was associated with increasing CEE/MPA dose ($p = 0.008$). An increase in complex partial seizure frequency also was associated with increasing CEE/MPA dose ($p = 0.05$). Two subjects taking lamotrigine had a decrease in lamotrigine levels of 25–30% while taking CEE/MPA.

Conclusions: CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. CEE/MPA may decrease lamotrigine levels. **Key Words:** Seizures—Epilepsy—Postmenopausal—Menopause—Hormone replacement therapy.

Unlike women of childbearing potential, postmenopausal women have stable reproductive hormone levels. When menstrual cycles no longer occur, the circulating hormonal profile is that of low estrogen and progesterone levels and elevated folliculin (follicle-stimulating hormone; FSH) and luteotropin (luteinizing hormone; LH) (1). Women with epilepsy of reproductive potential are at risk for anovulatory menstrual cycles (2) and catamenial seizure exacerbations (3). These risks, particularly catamenial seizure exacerbations, are likely caused by interactions between the epileptic brain and reproductive hormones in the brain. These risks are no longer relevant at menopause, and further, it has been reported that women with epilepsy may experience a decrease in seizure frequency at menopause, particularly if a catamenial exacerbation occurred in the reproductive years (4).

For postmenopausal women with epilepsy, hormone replacement therapy (HRT) presents another potential source of hormonal influence on seizure activity. The effect of HRT in women with epilepsy has not been systematically investigated. One survey suggests that it may exacerbate seizures (4). This would seem plausible, given that estrogen is proconvulsant in several animal models of epilepsy, including amygdalal kindling and pentylenetetrazol administration in ovariectomized rats (5). Estrogen induces the formation of new excitatory synapses in the CA1 region of the hippocampus, and further, this estrogenic induction involves activation of *N*-methyl-D-aspartate (NMDA) receptors (6). Increasing the complexity of hippocampal synaptic density is likely a mechanism for the proconvulsant activity of estrogen. Standard hormone replacement, which includes estrogen and a progestin, in postmenopausal women with epilepsy can be

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postulated to have an effect on seizures that is more evident than that of oral contraceptives in cycling women with epilepsy, because reproductive hormone levels during menopause are low and unchanging. Therefore the brain hormonal milieu in which exogenous hormones are introduced is markedly different in menopause from that in menstruating women.

Therefore the specific objective of this study was to determine in a prospective manner if standard HRT increases seizure frequency in postmenopausal women with epilepsy.

Subjects enrolled in this study met standard medical criteria for use of HRT prior to July 2002, which included no thromboembolic history or history of breast cancer, and were candidates for the routine use of HRT at the time for relief of menopausal symptoms and prevention of osteoporosis and cardiovascular disease. In July 2002, the results of the Women's Health Initiative (WHI) study altered the previously accepted standard for HRT use (7). The main findings were that HRT is not recommended as preventive treatment for asymptomatic women because the risks of HRT outweigh the benefits, because of increased risks of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism.

PATIENTS AND METHODS

This study was a randomized, placebo-controlled, double-blind clinical trial of the effect of HRT compared with placebo on seizure frequency in postmenopausal women with epilepsy. This study was approved by the Committees on Human Studies at the Weill Cornell Medical Center and at Beth Israel Deaconess Medical Center. The HRT chosen for this study was Prempro, which is 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate, designated here as CEE/MPA. CEE/MPA was used because it was the most widely prescribed form of HRT at the time of this study inception and therefore would give the broadest applicability to the results. A dose effect of CEE/MPA on seizure frequency was assessed by using two doses: a single and a double dose. Double-dose CEE/MPA has been used in clinical practice for further reduction in menopausal symptoms that persist with a single dose. Therefore the three treatment arms consisted of single-dose CEE/MPA, double-dose CEE/MPA, and placebo, with identical single daily dose capsules for each arm.

Study entry criteria were (a) having partial epilepsy and (b) being postmenopausal ($\geq$1 year without menses unless it was surgical menopause) confirmed by elevated LH and FSH levels, within 10 years of their last menstrual period. Subjects enrolled in this study met standard medical criteria for use of HRT prior to July 2002.

Subjects were recruited from the epilepsy practices at the Weill Cornell Medical Center and at Beth Israel Deaconess Medical Center. Data were collected at both sites and entered into a database at the Weill Cornell Medical Center. Subjects underwent a prospective 84-day baseline period on their stable optimal AED dosages. During the baseline phase, seizure frequency was documented, and hormone and AED levels were measured. Subjects were then randomized, and seizure occurrence was documented prospectively for the next 84 days, without alteration in AED dose. Study visits occurred every 4 weeks during the study. Safety of HRT use was monitored according to medically accepted gynecologic practice, which including clinically monitoring for thromboembolic events and uterine ultrasound or endometrial biopsy or both for breakthrough vaginal bleeding. The exit criterion for increased seizure frequency was a doubling of any baseline 28-day or 2-day seizure rate. If no seizures occurred during the baseline, exit criteria were two seizures during the treatment phase or one seizure if, in the opinion of the investigator, the subject should discontinue the study drug because of seizure activity.

Sample size was initially calculated with an estimate of seizure increase in 15% of the placebo-treated subjects, 30% of single-dose HRT-treated subjects, and 45% of the double-dose HRT–treated subjects, with a power of 80% and two-tailed significance level of 0.05. The estimated sample size was 40 subjects in each arm, for a total of 120 randomized subjects. However, recruitment was stopped after consideration of the WHI study results (7), and this report is on the recruited randomized subjects.

Randomization was generated in blocks of six, with two of each of the three treatment arms per block (placebo, single-dose CEE/MPA, and double-dose CEE/MPA) generated in a random order. The purpose of blocked randomization was to ensure an equal number of patients in the three study arms after every six patients, in the event that the study ended before the targeted accrual was complete. Furthermore, because it was unknown whether subjects with low versus high seizure frequency would respond differently to any effect of HRT on seizures, the randomization procedure was stratified by seizure severity. Three different strata of baseline seizure rates (none to one seizure/month, more than one to four seizures/month, and more than four seizures/month) were defined, and blocked randomization (as defined earlier with blocks of six) was performed within each seizure-frequency stratum. This procedure allows for an equal number of patients in the three study arms, within each seizure-frequency category. The study pharmacist encapsulated study drugs according to the randomized sequences in blocks of six and created study drug containers numbered sequentially with randomization numbers. Investigators and study coordinators enrolled subjects and assigned them to their seizure-frequency strata at the time of randomization (after the prospective baseline phase) and then randomized the subjects to study drugs/placebo sequentially within

the blocks of six assigned to that seizure-frequency stratum. All investigators and study coordinators remained blinded as to the treatment arm until the study database was completed and closed. Subjects also were blinded as to treatment arm. The biostatistician was aware of which subjects were in each treatment arm but remained blinded as to the exact treatment regimen of each arm. Only the study safety monitor and the study pharmacist, who encapsulated the study drug, had access to the unblinding code. Neither of these study personnel enrolled subjects or administered study drug. Unblinding by the study safety monitor was to be performed only in situations of medical necessity.

Baseline characteristics between treatment arms were compared by using univariate analysis of variance (ANOVA) or the nonparametric Kruskal–Wallis test, as appropriate. The primary end point of this study was to evaluate increased seizure activity (defined as yes/no) during HRT treatment, and this was assessed by comparing the proportion of subjects with increased seizure frequency between the three treatment arms. The χ^2 test for trend was used to examine the potential dose relation between treatment status (i.e., placebo, single dose, double dose) and increased seizure frequency (yes/no). Change in seizure frequency was determined by comparing the daily seizure rate during baseline with the daily seizure rate while the study drug was taken. The clinical impact of seizure increase was assessed by determining whether a subject had an increase in her most severe seizure type. Seizure severity has been shown to be one of the epilepsy-related factors, along with seizure frequency, to be significantly associated with decreased health-related quality of life (8,9). For example, if a subject's simple partial seizures increased in frequency, but the complex partial seizures did not, the subject was determined not to have a worsening of the most severe seizure type. The seizure types were ranked in descending order of severity as follows: generalized tonic–clonic > complex partial > simple partial. All p values are two-sided, with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SPSS v13.0 for Windows.

RESULTS

Subjects were recruited from September 2000 to June 2003, including 6 months of suspension of enrollment in 2002 because of the WHI results (7). The study was stopped in 2003 because of safety concerns raised by the WHI results (7). Eight subjects were in baseline at the time the study was stopped and are not reported on herein. During the study, three subjects withdrew consent during baseline because of the WHI results (7), and 11 subjects were enrolled in baseline but were not randomized because they did not meeting inclusion criteria, mostly because of not meeting criteria to take HRT safely. These reasons included history discovered during baseline of uterine fibroids, history of any thromboembolic disease or stroke, and virginity (making it difficulty to do an endometrial biopsy should abnormal bleeding occur). This remainder of this report is confined to the subjects who were randomized.

Twenty-one subjects were randomized after completing baseline. The subjects' ages ranged from 45 to 62 years (mean, 53 years; SD, ±5), and the age at last menstrual period ranged from 31 to 54 years (mean, 47 years; SD, ±5). The number of AEDs used ranged from none to three, with a median of one AED. All subjects had a diagnosis of partial epilepsy. During the study period, eight subjects had simple partial seizures, nine subjects had complex partial seizures, and three had secondarily generalized seizures.

Results are presented on all subjects who took any study drug during the trial. Six subjects were randomized to the placebo group; eight, to the single-dose CEE/MPA group; and seven, to the double-dose CEE/MPA group. The baseline characteristics are presented in Table 1. The number of seizures presented in Table 1 is the median, minimum, and maximum number for the entire baseline period in each treatment arm. No differences between treatment arms were present at baseline for age, age at menopause, number of AEDs, and all but one of the seizure-frequency categories. Simple partial seizures did attain statistical significance ($p = 0.04$), although the median number of simple partial seizures was near identical for the three groups (Table 1). The AEDs taken by subjects in each treatment arm are listed in Table 2.

Five subjects in the double-dose CEE/MPA arm discontinued before completion of the treatment period: one because of seizure increase after 39 days (met exit criteria); three because of HRT-related adverse effects after 30, 39, and 60 days, and all three also had increases in seizure frequency of either complex partial or secondarily generalized seizures; and one was lost to follow-up after 35 days of treatment (visit 1 of treatment phase). The subject lost to follow-up had no seizures during baseline or treatment. The subject who met exit criteria because of seizure increase did not have HRT-related side effects.

Seven subjects had no seizures of any type during baseline; one of these had a seizure during treatment. In no subject did a new or worsened seizure type develop than she had experienced before the study while taking the study drug. Seizure-frequency increases with HRT treatment were mild, and only one subject met the exit criteria of seizure-frequency doubling.

One subject in the single-dose CEE/MPA arm discontinued early after 32 days, because of HRT-related adverse effects, and she did not have seizure increase during treatment. Only one subject in the placebo arm discontinued early after 51 days of treatment, because of the WHI study results and stopping of this study; she had no seizures during baseline or treatment periods. The

TABLE 1. *Characteristics of subjects in each treatment arm (N = 21) with number of seizures during 84-day baseline period*

Treatment group	Mean age in (yr) ± SD[a]	Mean menopausal age in (yr) ± SD[b]	No. of simple partial seizures (median; min, max)[c]	No. of complex partial seizures (median; min, max)[d]	No. of generalized seizures (median; min, max)[e]	No. of total seizures (median; min, max)[f]	No. of AEDs (median; min, max)[g]
Placebo (n = 6)	53.5 ±2.6	45.6 ±8.4	0; 0, 0	0; 0, 5	0; 0, 3	1; 0, 5	2; 0, 2
Single CEE/MPA (n = 8)	52.1 ±5.8	47.9 ±3.4	0; 0, 16	1; 0, 19	0; 0, 0	1; 0, 19	1; 1, 2
Double CEE/MPA (n = 7)	52.1 ±5.2	47.0 ±5.1	1; 0, 189	0; 0, 7	0; 0, 1	2; 0, 189	1; 1, 3

[a] p = 0.85 by ANOVA test.
[b] p = 0.80 by ANOVA test.
[c] p = 0.04 by Kruskal–Wallis test.
[d] p = 0.41 by Kruskal–Wallis test.
[e] p = 0.20 by Kruskal–Wallis test.
[f] p = 0.43 by Kruskal–Wallis test.
[g] p = 0.30 by Kruskal–Wallis test.

HRT-related adverse effects resulting in discontinuation included headache, vaginal spotting, and pelvic discomfort.

The association of increased seizure frequency with increasing CEE/MPA dose was significant for an increase in seizure frequency of any seizure type after HRT treatment ($p = 0.05$ by χ^2 test for trend) (see Table 3). Further, the association of increased complex partial seizure frequency with increased CEE/MPA dose also was significant ($p = 0.05$) (Table 3). The association of increased most-severe seizure type with increased CEE/MPA dose was significant ($p = 0.008$). Because of curtailment of enrollment, comparison of seizure-frequency change by seizure-frequency strata could not be performed.

Little change in AED levels was associated with treatment arms, although the numbers of subjects taking specific AEDs was small. In the two subjects randomized to CEE/MPA who also were taking lamotrigine (LTG), a consistent directional change was found. In one subject receiving polytherapy, LTG levels declined from a mean of 9.6 μg/ml (range, 10.1–9.2) during baseline, to a mean of 7.7 μg/ml (range, 6.4–8) during treatment, with no change in seizures. In another subject receiving monotherapy, the LTG levels declined from a mean of 2.1 μg/ml (range, 2.6–1.5) during baseline to a mean of 1.4 μg/ml (range, 1.3–1.5) during treatment, and this subject did have increased seizures during treatment. Therefore LTG levels declined by 25–30% in these subjects. Both subjects were in the single-dose CEE/MPA treatment arm.

Because in one subject, the seizure increase could be explained by a decrease in LTG levels, statistical analyses were repeated, eliminating this subject from the analysis, and the results showed no material change.

TABLE 2. *AEDs in each treatment arm*

Treatment arm	Placebo	Single-dose CEE/MPA	Double-dose CEE/MPA
AEDs	PRM, PB	PRM	TPM, CBZ, TGB
	PB	PHT	VPA, CZP
	CBZ, VPA	CBZ, PHT	PHT
	PB, PHT	TPM, LTG	PHT
	LTG, LEV	LEV	CZP
	None	GBP	GBP
		LTG	VPA
		TPM, PHT	

AED, antiepileptic drug; CBZ, carbamazepine; CZP, clonazepam; GBP, gabapentin; LTG, lamotrigine; LEV, levetiracetam; PB, phenobarbital; PHT, phenytoin; PRM, primidone; TPM, topiramate; TGB, tiagabine; VPA, valproic acid.

DISCUSSION

These findings provide evidence that CEE/MPA is associated with dose-related increases in seizure frequency in postmenopausal women with epilepsy. Although recruitment into this study was curtailed by the results of the WHI study and the number of subjects necessary to prove that seizure frequency was increased with each seizure type was not obtained, the available data show that seizure occurrence increased with CEE/MPA use in a dose-related manner.

Seizure increase is thought to be due to the estrogenic component of HRT; however, this protocol cannot distinguish between the effect of estrogen or medroxyprogesterone acetate on seizure activity. More scientific evidence exists for the seizure-promoting potential of estrogen. It cannot be ruled out, however, that brain exposure to increased synthetic progestin may have been related to seizure activity.

The decrease in LTG levels with HRT use is consistent with previous reports of decreased LTG levels during oral contraceptive use and with pregnancy (10–13). Increased LTG clearance in the setting of elevated circulating reproductive hormones is thought to be due to effects on the glucoronidation pathway of LTG metabolism, leading to a mean decrease in levels of >50% during oral contraceptive use (10) and an increase in clearance of 40–330% during pregnancy (11–13).

TABLE 3. *Number of subjects with increase in seizure frequency by treatment arm (N = 21)*

Treatment group	Simple partial[a]		Complex partial[b]		Secondarily generalized		Total no. Sz[c]		Any Sz type[d]		Most severe Sz type[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Placebo (n = 6)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)
Single CEE/MPA (n = 8)	3	(37.5)	1	(12.5)	0	(0.0)	3	(37.5)	4	(50.0)	3	(37.5)
Double CEE/MPA (n = 7)	1	(14.3)	3	(42.9)	1	(14.3)	3	(42.9)	5	(71.4)	5	(71.4)

[a] $p = 0.88$ by χ^2 test for trend.
[b] $p = 0.05$ by χ^2 test for trend.
[c] $p = 0.10$ by χ^2 test for trend.
[d] $p = 0.05$ by χ^2 test for trend.
[e] $p = 0.008$ by χ^2 test for trend.

This study, although limited in its ability to be generalized because of both the small number of subjects in this study and the precipitous decline of HRT use, provides information about the potential detrimental effect of CEE/MPA on seizures for women with epilepsy and supports the previously reported survey results (4).

Certainly women with epilepsy have taken HRT in the past without seizure exacerbations and will need to do so in the future for short-term management of menopausal symptoms, specifically hot flashes, insomnia, and vaginal atrophy. This study does not imply a contraindication to HRT in women with epilepsy but does suggest that CEE/MPA may not be the optimal HRT regimen for women with epilepsy. Possibly a safer HRT regimen in women with epilepsy would be an estrogen along with natural progesterone (14,15). This may be particularly appropriate for women with epilepsy because natural progesterone has neuroactive metabolites such as allopregnanolone, which has been shown to be a potent positive allosteric modulator at the γ-aminobutyric acid (GABA) receptor (16–18). Statistically significant findings in open-label investigations suggest that natural progesterone supplement may reduce seizure frequency in women with catamenial epilepsy (19,20). No reports of effect of the synthetic progestin used in this study, medroxyprogesterone acetate, on seizure threshold are available.

These results also raise the possibility that HRT decreases LTG levels, which may have clinical significance for some patients. This is likely due to the same mechanism as is present when LTG levels decline in the setting of pregnancy and oral contraceptive use.

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