MORE IS NOT BETTER: HORMONES FOR MENOPAUSAL WOMEN WITH EPILEPSY?

Hormone Replacement Therapy in Women with Epilepsy: A Randomized, Double-Blind, Placebo-Controlled Study. Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, Labar DR, Hauser WA. *Epilepsia* 2006;47(9):1447–1451. 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.

COMMENTARY

The possible effect of reproductive hormones on seizures was recognized over 2,000 years ago. Clinical observations of a relationship between the menstrual cycle and seizure occurrence in women of reproductive age were cited in medical journals as early as the turn of the 19th century. In 1942, experimental work in rats demonstrated the anticonvulsant properties of progesterone (1). Since then, many animal studies have confirmed the effects of progestins and estrogens on seizure threshold and epileptogenesis. Many cellular and molecular mechanisms contribute to the changes in brain excitability mediated by these hormones. Although an oversimplification, studies generally support the finding that the estrogens have proconvulsant properties and progestins have anticonvulsant properties. The three principal circulating estrogens are estrone, estradiol, and estriol. The progestins include progesterone and progesterone derivatives. Dihydroprogesterone is the immediate 5-α-reduced metabolite of progesterone and is further metabolized to allopregnanolone (3α-hydroxy-5α-pregnan-20-one), a $GABA_A$-receptor–modulating neurosteroid (1,2). Much of the antiseizure effect of progesterone may be due to the conversion to this metabolite, and synthetic progestins are not converted to this or other known neurosteroids.

The findings of experimental studies parallel nicely the clinical observation that seizure frequency is increased in many women with epilepsy in association with certain phases of the menstrual cycle (catamenial epilepsy). In women with localization-related epilepsy, 39% demonstrate a catamenial pattern (3). The patterns described correlate with phases of relatively high estrogen/progesterone ratios: perimenstrual and periovulation in normal menstrual cycles and throughout the inadequate luteal phase in anovulatory cycles. Additionally, an open-label treatment trial with supplemental progesterone in women ($n = 25$) demonstrated a 54% decline in the average frequency of daily complex partial seizures ($p < 0.01$) and a 58% decline in secondarily generalized tonic–clonic seizures ($p < 0.02$) (4). Nonetheless, no Class I evidence is available for the benefits of progesterone use in women with epilepsy during the reproductive years, although a multicenter, double-blind, randomized, placebo-controlled trial is currently underway (3).

Understanding the effects of endogenous and exogenous reproductive hormones on seizure control during the perimenopausal transition and postmenopause has been more elusive. Perimenopause is marked by erratic and frequently high estrogen levels, while postmenopause is characterized by stable,

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low estrogen levels (5). Studies in women during these later life stages are very limited. Previously, Harden et al. performed a retrospective questionnaire study of perimenopausal and postmenopausal women with epilepsy ($n = 81$) (6). Their findings suggest that seizure frequency can increase with perimenopause and can improve once the menopausal transition is complete, especially for women who had a catamenial pattern to her seizures. In the postmenopausal group, hormone replacement therapy (HRT) was significantly associated with an increase in seizures.

The present study by Harden et al. explores the effects of the combination of conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA) at two different doses, using a design that meets criteria for Class I evidence (i.e., double-blind, placebo-controlled, randomized trial). Several factors distinctive to the study design may have enhanced the likelihood of a positive finding regarding the effect of the combination hormonal treatment on seizure frequency. The authors astutely remark that postmenopausal women may be more susceptible to the effects of exogenous hormones on seizures, given that their hormonal milieu is one of low and stable estrogen and progesterone levels. Estrone is the primary estrogen after menopause, with its main source from subcutaneous fat. Each of the estrogens has distinct biological actions, although individual effects on seizure frequency are unknown. Similarly, the various equine estrogens are likely to have distinct actions from physiologic forms of estrogen in women, and the complex mixture of CEE extracted from horses includes androgens and progestins (1). CEE/MPA was commonly used as hormone replacement therapy at the time this trial was initiated. Moreover, the investigators utilized an elegant approach of randomizing a third of the patients to double-dose CEE/MPA, which was a common prescription dose for menopausal women who did not have symptom relief with single-dose CEE/MPA.

The Harden et al. trial was ended early because of results from the Women's Health Initiative study ($n = 16{,}608$). It was a shock to the medical community that not only was HRT not a useful preventive medicine tool, but it could actually increase the risk for invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism (7). The Harden et al. study initially predicted that 120 women, 40 in each treatment arm, would be needed for a power of 80% and a two-tailed significance level of 0.05. Because recruitment had to be terminated, only 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 groups were similar by other characteristics, except that the frequency of simple partial seizures was higher in the double-dose CEE/MPA group, which may have influenced the outcome data. What is truly remarkable is that despite discontinuing the study prematurely and limited enrollment, the results were still positive and even were able to demonstrate statistical significance for a dose-related response for CEE/MPA and increased seizure frequency.

After the report of the Women's Health Initiative study, the prescriptions for oral HRT in the United States decreased by approximately one-third by June 2003, from their peak in 2000. However, 59.6 million prescriptions for these products were still dispensed in 2003, another 7.5 million dispensed for transdermal products, and an additional 8.9 million for oral progestins (8). Although long-term HRT is no longer recommended for health maintenance, short-term HRT is still prescribed for the management of menopausal symptoms, such as hot flashes, insomnia, and vaginal atrophy (9). Thus, the findings of the Harden et al. study remain clinically relevant. Updated results of dispensing practices are not yet available; however, the search for products for menopausal symptom relief continues and has moved firmly into the alternative therapy arena (10,11). The possible effects of various alternative agents on seizure threshold are not known.

Although the Harden et al. trial cautions against use of CEE/MPA in postmenopausal women with epilepsy, it cannot differentiate between the possible effects of the many different equine estrogens, equine androgens, or even the equine progestins and synthetic progestin MPA. In addition, a possible confounder is that in the two lamotrigine-treated patients, lamotrigine levels decreased by 25% to 33% with single-dose CEE/MPA. No changes were observed in other antiepileptic drug levels, but the number of subjects on each AED was small. A possible alternative to the CEE/MPA combination medicine may be one that uses a more pure human-like estrogen derivative, such as estradiol or possibly estrone, and natural progesterone, which can be metabolized to the beneficial neurosteroid allopregnanolone.

The early termination of this trial resulted in limited enrollment and may have reduced it to a Class II study, as there were a high percentage of subjects who discontinued, many subjects who were evaluated after just 30 to 60 days, a higher number of simple partial seizures in the double-dose group, and comparisons by seizure-frequency strata could not be performed, as originally planned. The investigators state that the seizure frequency increases were mild, but details were not provided; any increase in daily seizure rate from baseline was counted as a positive response. It would have been helpful if the authors had reported on the magnitude of seizure increases, as it could help put their findings into the context of everyday treatment decisions and patient counseling.

Nonetheless, having Class I or Class II evidence from a treatment trial assessing the influence of reproductive hormones on seizures in humans is unique at this point in time. These findings further the understanding of the impact of hormones on seizure control in women with epilepsy, and the principles learned can be extended to other life epochs, including puberty, menstrual cycles, pregnancy, and perimenopause. Future studies on whether other estrogens with natural progesterone could

circumvent the risk for increased seizures would be beneficial for postmenopausal women with epilepsy.

by Page B. Pennell, MD

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Nonconvulsive Seizures in the Pediatric Intensive Care Unit: Out of Sight, Out of Mind?

Nonconvulsive Seizures in the Pediatric Intensive Care Unit: Etiology, EEG, and Brain Imaging Findings. Saengpattrachai M, Sharma R, Hunjan A, Shroff M, Ochi A, Otsubo H, Cortez MA, Carter Snead O III. *Epilepsia* 2006;47(9):1510–1518. PURPOSE: To determine the occurrence of nonconvulsive seizures (NCS) in the Pediatric Intensive Care Unit (PICU); to ascertain the relationship of NCS to past medical history, etiology, EEG, and brain imaging; and to determine the concordance between abnormal EEG findings and neuroimaging abnormalities. METHODS: A retrospective review was conducted of all pediatric patients who were admitted or transferred to the PICU from January 2000 to December 2003 with an unexplained decrease in level of consciousness, no overt clinical seizures, and EEG recordings performed within the 24 hours of onset of an altered state of consciousness. RESULTS: Twenty-three of 141 patients who met criteria for inclusion in the study (16.3%) were found to have NCS. The male-to-female ratio was 1.9:1. The largest group of patients (43%) had no preexisting neurological condition prior to the onset of NCS. In the remainder, the etiology of NCS included: acute structural brain lesion (48%), acute nonstructural brain lesion (22%), epilepsy-related seizure (13%), and others (17%). Epileptic foci were lateralized to the right side in 39.2%, the left side in 30.4%, and were bilateral in 30.4%. Of 23 patients with NCS, 18 (78.3%) demonstrated abnormal neuroimaging. In 10 of 18 of these patients (55.6%), the findings on neuroimaging were concordant with the lateralization found on EEG ($p < 0.05$, Fisher's exact test). CONCLUSIONS: NCS are not uncommon in pediatric patients with an altered state of consciousness. Almost half of the patients were previously healthy especially if they were under 6 months of age. This report highlights the importance of clinical awareness of NCS in the PICU.

Nonconvulsive Status Epilepticus in Children: Clinical and EEG Characteristics. Tay SK, Hirsch LJ, Leary L, Jette N, Wittman J, Akman CI. *Epilepsia* 2006;47(9):1504—1509. BACKGROUND: Nonconvulsive status epilepticus (NCSE) is a highly heterogeneous clinical condition that is understudied in the pediatric population. OBJECTIVE: To analyze the epidemiological, clinical, and electroencephalograpic features in pediatric patients with NCSE. METHODS: We identified 19 pediatric patients with NCSE

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from the epilepsy database of the Comprehensive Epilepsy Center at Columbia University between June 2000 and December 2003. Continuous EEG monitoring was analyzed and chart review was performed. RESULTS: The patients ranged from 1 month old to 17 years of age. Five patients developed NCSE following convulsive status epilepticus (CSE), and a further 12 patients developed NCSE after brief convulsions. Two developed NCSE as the first manifestation during a comatose state following hypoxic events. Acute hypoxic-ischemic injury was the most frequent etiology of NCSE in our population (5 of 19; 26%), followed by exacerbation of underlying neurometabolic disease (4 of 19; 21%), acute infection (3 of 19; 16%), change in antiepileptic drug regimen (3 of 19; 16%), refractory epilepsy (2 of 19; 11%), and intracranial hemorrhage (2 of 19; 11%). Six patients had associated periodic lateralized epileptiform discharges (PLEDs), one had generalized periodic epileptiform discharges (GPEDs). Five (5 of 19; 26%) patients died of the underlying acute medical illness. Periodic discharges were associated with worse outcome. CONCLUSIONS: The majority of our patients with NCSE had preceding seizures in the acute setting prior to the diagnosis of NCSE, though most of these seizures were brief, isolated convulsions (12 patients) rather than CSE (five patients). Prolonged EEG monitoring to exclude NCSE may be warranted in pediatric patients even after brief convulsive seizures. Prompt recognition and treatment may be necessary to improve neurological outcome.

COMMENTARY

Although the magnitude of risk associated with nonconvulsive seizures (NCS) is controversial, laboratory studies (1) and clinical experience (2) suggest that these seizures can result in neurological injury, especially if they are prolonged. Furthermore, the clinical manifestations related to NCS, including confusion, lethargy, and unresponsiveness are likely to be mistakenly attributed to alternative causes, leading to unnecessary evaluations, prolonged intensive care unit stays, and inappropriate interventions. Thus, the finding of NCS as a cause of a patient's encephalopathy could have a major impact not only on their intensive care unit management but on their long-term management as well. The prevalence of NCS in critically ill adults has been described recently in reports that make it clear that this entity has been underrecognized (3,4). However, the prevalence and clinical features of NCS in children had not been addressed until Saengpattrachai et al. and Tay and colleagues reported on the extent of the problem of unrecognized NCS in hospitalized children, as reviewed here. At first glance, their findings appear to be partially discrepant but this discrepancy likely reflects the fact that the studies use different technologies and evaluate slightly different clinical questions.

Saengpattrachai and colleagues obtained routine EEG studies (lasting at least 30 minutes) from pediatric patients who were transferred to the intensive care unit for a reduced level of consciousness. None of 141 patients was found to be in nonconvulsive status epilepticus, though a significant minority had NCS that were frequent enough to be captured during the brief studies. EEG seizures were usually focal, often with concordant neuroimaging. Treatment appeared to abolish the seizures, as documented by follow-up routine EEG studies.

Tay et al. addressed the question of which patients in the pediatric intensive care unit are at risk for nonconvulsive status epilepticus by monitoring all patients using continuous EEG (lasting at least 12 hours) and then determining which patients met specific EEG criteria for nonconvulsive status epilepticus. As the authors note, the EEG criteria were tightly defined so as to ensure that the patients included had continuous electrographic seizures. The criteria may well have led to exclusion of some patients who had frequent seizures yet did not quite meet the rigid EEG standards for nonconvulsive status epilepticus. They found that 10% of all monitored patients were in nonconvulsive status epilepticus. They assessed the clinical setting, EEG patterns, imaging, and outcome in patients meeting the EEG criteria for nonconvulsive status epilepticus. Most (but not all) patients with nonconvulsive status epilepticus had observed convulsive seizures at some time during hospitalization prior to the diagnosis, though only three had been in convulsive status epilepticus. Most had identifiable, acute precipitants. The EEG pattern was variable but included rhythmic epileptiform discharges or rhythmic slowing, which was focal in all but four patients.

As each group notes, the studies do not allow for definitive conclusions on the prevalence of NCS or nonconvulsive status epilepticus in the pediatric intensive care unit. Both studies are limited by retrospective analysis and the potential for selection bias. For example, it is likely that the patients in the Tay et al. study underwent continuous EEG monitoring based on clinical factors suggesting a heightened risk for seizures. If all patients with unexplained encephalopathy were monitored, the "hit rate" might have been lower than 10%. However, it also is likely that continuous nonconvulsive seizure activity is more common than one would think based on the report of Saengpattrachai and colleagues. As these authors state, the brief EEGs may have failed to identify times when electrographic seizure activity became continuous. In fact, one patient had an 11-minute seizure during the routine EEG study. In light of these pediatric studies and similar studies in adults (3,4), it seems plausible that frequent NCS, including nonconvulsive status epilepticus, contribute to the clinical findings in a significant minority of children with unexplained encephalopathy.

In addition to supporting the possibility that NCS may be a commonly unrecognized cause of cognitive deterioration in children, these reports may help formulate an approach to evaluating children with unexplained encephalopathy. While a routine EEG recorded for at least 30 minutes appeared adequate to make a diagnosis in the patients studied by Saengpattrachai and colleagues, it is impossible to know whether additional patients would have been identified with longer recording sessions. A pragmatic approach would be to start with a routine EEG but to consider a continuous 24-hour recording in patients at high risk for ongoing NCS, such as those who have had previously observed convulsive seizures. Both groups found that the NCS were variable in EEG pattern but most often focal. Thus, EEG monitoring for detection of NCS should typically include full international 10–20 electrode placements rather than expedient alternatives that are less spatially sensitive.

All patients demonstrating NCS were treated, leading to resolution of the previously unrecognized seizures. As the authors for both studies note, this finding does not allow one to draw conclusions as to the magnitude of benefit that the patients derived from having an accurate diagnosis. Given the evidence that NCS can result in permanent neurological dysfunction (2), however, it seems prudent to aggressively identify patients with this readily treatable condition.

by Paul Garcia, MD

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Treatment Options for Hypothalamic Hamartomas—No Laughing Matter

Surgical Management of Hypothalamic Hamartomas with Epilepsy: The Stereoendoscopic Approach. Procaccini E, Dorfmuller G, Fohlen M, Bulteau C, Delalande O. *Neurosurgery* 2006 Oct;59(4 Suppl 2):ONS336–ONS346. OBJECTIVE: Hypothalamic hamartomas (HHs) require surgical treatment in patients presenting with refractory epilepsy. METHODS: The authors report on a single-center series of 33 patients (24 males, 9 females) who underwent surgery between January 1997 and April 2004. They experienced several types of seizure (gelastic, tonic, partial, atonic, generalized tonic-clonic, dacrystic, infantile spasm, mental retardation, and behavioral and endocrinological abnormalities). Forty-nine interventions were carried out. Every patient, with the exception of the first, underwent hamartoma disconnection (pterional approach, six patients; endoscopy, 15 patients; both, 11 patients). The endoscopic approach was carried out with a frameless stereotactic system to enhance feasibility and efficacy of the disconnecting procedure. RESULTS: Surgery-related neurological complications occurred in two patients, both after a pterional microsurgical approach. Furthermore, two patients experienced panhypopituitarism and one patient experienced transitory central insipid diabetes. All patients but one showed recovery or considerable improvement of their epilepsy (Engel Class 1, 48.5%; Engel Class 2, 3%; Engel Class 3, 45.5%; mean follow-up duration, 1 year 7 months). CONCLUSIONS: According to the proposed classification of sessile HH into four types, the best candidates for endoscopic disconnection are Type 2 and Type 3 HHs. In the present series, 90% of patients affected by Type 2 HH became seizure-free and the remaining 10% improved; of those with Type 3 HH at presentation, 35.3% recovered and 60% improved. Neuropsychological and endocrinological test results showed improvement in many patients. Data from our series demonstrate that frameless stereotactic endoscopic disconnection should be considered as the treatment of choice in the presence of favorable anatomic conditions.

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COMMENTARY

Hypothalamic hamartomas represent one of the least common causes of medically intractable epilepsy, yet it can hardly be considered an orphan disease. Worldwide interest in this unusual form of cortical dysplasia, particularly within the neurosurgical community, has blossomed over the last 5 years as a result of a newfound understanding of the pathophysiology of the epileptogenesis and more importantly, on the success of a variety of elegant and sophisticated high-tech surgical approaches to treating the disease.

Hypothalamic hamartomas are nonneoplastic overgrowths of normal appearing tissue comprised of disorganized neurons and glia that are lacking the enlarged "balloon cells" characteristic of focal cortical dysplasia (1). Most occur sporadically, although 10% are associated with Pallister-Hall syndrome (1). Based on the anatomic relationship between the hamartoma and the hypothalamus, they can be divided into two main subtypes—pedunculated and sessile. The pedunculated lesions do not arise within the hypothalamus but attach with a narrow base and project outside the ventricle. These lesions are less often associated with seizures and more likely present with precocious puberty. Neuropsychological compromise is less frequent. Precocious puberty can be treated medically with gonadotrophin-releasing hormone (GnRH) agonists and require surgery only when resistant. Although hamartomatous cells stain for GnRH, it is unclear if they release GnRH or transforming growth factor-α, which is trophic for release of GnRH from normal hypothalamus (1). In contrast, the sessile lesions lie within the hypothalamus and often cause seizures and variable degrees of mental retardation and aggressive behavior, particularly if the seizures are not well controlled. Seizures consist of gelastic attacks, which can evolve into drop attacks, tonic, tonic–clonic, and secondarily generalized seizures. Whole-cell recordings from these hamartomas have shown that most cells are small GABAergic inhibitory neurons that exhibit intrinsic pacemaker-like behavior (2). Precocious puberty also occurs with sessile lesions.

Initially, the etiology of the seizures associated with hypothalamic hamartomas was unclear. However, based on ictal perfusion studies and depth electrode recordings, it became clear that the seizures arose from intrinsic epileptogenicity of the hypothalamic hamartoma itself (3,4). Although the first surgical excision was performed as early as 1969 (5), even later attempts to remove these lesions from below with a subtemporal, subfrontal, or pterional approach met with high complication rates. More success was obtained removing the lesions from above using a transcallosal, interforniceal approach, first popularized by Rosenfeld (6). Using this approach, rates of seizure-freedom are as high as 54% with 90% having a 90% reduction in seizure frequency (7). Permanent morbidity rates, however, are not insignificant with 8% diabetes insipidus, 8% memory impairment, 4% hemianopsia, and 19% hyperphagia (7).

Less invasive methods of eradicating the hypothalamic hamartomas include radiofrequency thermoablation (8), interstitial brachytherapy (9), and stereotactic radiosurgery (10). The latter technique reports seizure-free rates of 37% after a delay of 6–12 months with 60% having a dramatic reduction in seizures and no permanent complications (10). However, the adverse effects of radiation may take several years to manifest. Although promising, this modality may be useful only for smaller lesions, which also have the best surgical outcome.

The stereoendoscopic technique described by Procaccini et al. introduces yet another treatment option for consideration. The authors have modified the Rosenfeld transcallosal approach and made it less invasive by using an endoscope passed through the foramen of Monro. In addition, drawing on the theoretical basis for the functional hemispherectomy, the authors argue that a disconnection of the hamartoma from the hypothalamus should be sufficient to eliminate seizures and a complete resection is not required. However, based on the anatomy of the lesion, the endoscopic approach alone is only applicable in 50% of their cases, whereas the remaining patients required an additional pterional craniotomy to disconnect those parts of the hamartoma that could not be reached from above. Overall a 49% seizure-free rate was reported with 97% showing improvement, although multiple surgeries were required for several patients. In their study, complications were associated only with the open pterional procedure (27%) and not with the stereoendoscopic approach. However, a more recent presentation revealed a complication rate of 10% for the stereoendoscopic approach (11).

How is the referring physician to decide between these seemingly similar treatment options? As with most surgical lesions, the easy ones are easy and the hard ones are hard, regardless of the surgical approach. Clearly, the small lesions within the third ventricle can be effectively managed using either modality, with a similar outcome with respect to seizure-freedom and complications. Currently, the choice of surgical procedure will depend on the abilities and confidence of the treating surgeon. The approaches that are most technically demanding can be difficult to proliferate to other centers. Radiosurgery is less "operator dependent" and may be a reasonable treatment in lower volume centers. Whether late complications arise from radiosurgery remains unknown and will require additional follow-up studies to determine. Minimally invasive endoscopic approaches have been shown to offer real advantages over open surgery in minimizing morbidity and are becoming the standard of care in the treatment of diseases, such as colloid cysts, pituitary adenomas, and noncommunicating hydrocephalus. As endoscopic microinstrumentation continues to improve, this modality will play an increasing role in the treatment of hy-

pothalamic hamartomas, perhaps in combination with endoscopic approaches from below, either through an eyebrow incision or an extended transsphenoidal route. Indeed, at a recent medical meeting, the authors, previously espousing the open transcallosal approach, presented data in favor of the minimally invasive endoscopic approach (12).

Although it has been said that "laughter is the best medicine," it appears that medicine is finally besting laughter.

by Theodore H. Schwartz, MD, FACS

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Oxcarbazepine and Carbamazepine: Expected and Unexpected Differences and Similarities

Effects of Carbamazepine and Oxcarbazepine on the Reproductive Endocrine Function in Women with Epilepsy. Lofgren E, Tapanainen JS, Koivunen R, Pakarinen A, Isojarvi JI. *Epilepsia* 2006;47(9):1441–1446. PURPOSE: The aim of the study was to compare the effects of carbamazepine (CBZ) and oxcarbazepine (OXC) on the reproductive endocrine function in women with epilepsy. OXC is a novel antiepileptic drug (AED), and the occurrence of reproductive dysfunction in women treated with OXC monotherapy for epilepsy has not been studied previously. METHODS: Thirty-five women with epilepsy were examined in the Department of Neurology at Oulu University Hospital. Sixteen patients were treated with CBZ monotherapy, and nineteen patients were treated with OXC monotherapy. The subjects were clinically examined, vaginal ultrasonography was performed, and serum sex hormone concentrations were measured. RESULTS: The women taking CBZ or OXC had lower serum testosterone (T) levels and lower free androgen indexes (FAIs) than the control subjects. CBZ medication was associated with increased concentrations of serum sex hormone–binding globulin (SHBG). The patients taking OXC had higher concentrations of dehydroepiandrosterone sulfate (DHEAS) and androstendione (A) than did the women taking CBZ. Moreover, the prevalence of polycystic ovaries (PCOs) was high in the OXC-treated women. CONCLUSIONS: CBZ and OXC have different effects on the reproductive endocrine function. Although both drugs were associated with low serum T concentrations and low FAIs, only OXC was associated with a high frequency of elevated levels of A and DHEAS and with an increased prevalence of PCOs. These findings suggest that OXC may be disadvantageous for women with epilepsy and hyperandrogenism, whereas CBZ may be beneficial for these women.

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COMMENTARY

Oxcarbazepine is a structural analog of carbamazepine that follows a different metabolic pathway, resulting in several clinical advantages. Unlike carbamazepine, which is converted to an epoxide metabolite, oxcarbazepine is rapidly converted to its monohydroxy derivative (MHD), which is the main active metabolite. Oxcarbazepine, MHD, and carbamazepine all share a principal mechanism of action, which is the blockade of voltage-gated sodium channels. However, there are small differences in other mechanisms—mainly that MHD blocks N/P- and R-type calcium channels, while carbamazepine blocks L-type calcium channels (1). MHD has several pharmacokinetic advantages over carbamazepine, including absence of autoinduction, much less pronounced and more selective induction of P450 enzyme system, and absence of interaction with agents, such as erythromycin or propoxyphene, that result in excessive accumulation of carbamazepine. Based on known pharmacokinetics, predictions have been made regarding other differences and similarities between the two agents; however, studies have not always supported expectations.

As a result of its pharmacokinetic advantages, oxcarbazepine was presumed to have fewer adverse effects on endocrine function than carbamazepine (1). One notable exception has been the finding that serum sodium decreased when carbamazepine was replaced with oxcarbazepine (2), and hyponatremia was more common with oxcarbazepine than carbamazepine therapy (3). As a potent inducer of P450 enzymes, carbamazepine use has been associated with a number of hormonal alterations, including lower thyroxine levels (4), elevated levels of sex hormone binding globulin, and lower free testosterone levels in men (5). Because of the much less pronounced enzyme induction with oxcarbazepine, it was presumed that abnormalities resulting from enzyme induction by carbamazepine would be reversed if the patient were switched to oxcarbazepine. Indeed, lower thyroxine levels caused by carbamazepine increased after replacement with oxcarbazepine (6). Similarly, the effect of oxcarbazepine on sex hormones in men appears to be favorable in comparison to carbamazepine. In one study, replacing carbamazepine with oxcarbazepine was associated with reduction of serum sex hormone binding globulin and an increase in serum dehydroepiandrosterone sulphate (7). In another study, oxcarbazepine produced no hormonal alterations at doses lower than 900 mg per day, but was associated with elevated levels of testosterone and sex hormone binding globulin at daily doses of 900 mg per day or greater (8).

In addition, chronic carbamazepine use has been associated with reduced bone density (9). It was presumed that oxcarbazepine would be less likely than carbamazepine to increase bone turnover and reduce bone density. However, a formal study showed that in comparison to controls, patients taking either oxcarbazepine or carbamazepine had lower 25-hydroxyvitamin D levels as well as an elevation of a bone-formation marker that predicts loss of bone mass over time (10). Another study of patients treated with carbamazepine or oxcarbazepine for more than 1 year also demonstrated reduced bone density in both groups in comparison to normal controls (11).

The current study by Lofgren et al. found somewhat unexpected similarities and differences between oxcarbazepine and carbamazepine. Both carbamazepine- and oxcarbazepine-treated women had lower serum bioactive testosterone and progesterone levels than the control subjects, and the testosterone level reduction was independent of the oxcarbazepine dose. In contrast, the prevalence of polycystic ovaries (but not the polycystic ovary syndrome) was higher in the oxcarbazepine-treated women, as were levels of two weak androgens, dehydroepiandrosterone sulfate and androstenedione. The clinical significance of these findings is not known. The authors indicated that the incidence of polycystic ovaries in the study was higher than previously reported, which raises the possibility of preferential recruitment of women with menstrual disorders, who may have been more willing to participate in the study than women without menstrual disorders. The definitive assessment of the effect of oxcarbazepine on reproductive endocrine function must come from a prospective study of patients recruited and evaluated before and periodically after initiation of treatment with oxcarbazepine.

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