

# 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.

Epilepsy Currents, Vol. 7, No. 3 (May/June) 2007 pp. 74–76

Blackwell Publishing, Inc.

© American Epilepsy Society

## 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.

by Bassel W. Abou-Khalil, MD

## References

1. Schmidt D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? *Epilepsy Behav* 2004;5:627–635.
2. Isojarvi JI, Huuskonen UE, Pakarinen AJ, Vuolteenaho O, Myllyla VV. The regulation of serum sodium after replacing carbamazepine with oxcarbazepine. *Epilepsia* 2001;42:741–745.
3. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005;65:1976–1978.
4. Isojarvi JI, Pakarinen AJ, Ylipalosaari PJ, Myllyla VV. Serum hormones in male epileptic patients receiving anticonvulsant medication. *Arch Neurol* 1990;47:670–676.
5. Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Kelly KM, Farina EL, Frye CA. Differential effects of antiepileptic drugs on sexual function and reproductive hormones in men with epilepsy: interim analysis of a comparison between lamotrigine and enzyme-inducing antiepileptic drugs. *Epilepsia* 2004;45:764–768.
6. Isojarvi JI, Airaksinen KE, Mustonen JN, Pakarinen AJ, Rautio A, Pelkonen O, Myllyla VV. Thyroid and myocardial function after replacement of carbamazepine by oxcarbazepine. *Epilepsia* 1995;36:810–816.

7. Isojarvi JI, Pakarinen AJ, Rautio A, Pelkonen O, Myllyla VV. Serum sex hormone levels after replacing carbamazepine with oxcarbazepine. *Eur J Clin Pharmacol* 1995;47:461–464.
8. Rattya J, Turkka J, Pakarinen AJ, Knip M, Kotila MA, Lukkarinen O, Myllyla VV, Isojarvi JI. Reproductive effects of valproate, carbamazepine, and oxcarbazepine in men with epilepsy. *Neurology* 2001;56:31–36.
9. Kumandas S, Koklu E, Gumus H, Koklu S, Kurtoglu S, Karakucukcu M, Keskin M. Effect of carbamazepine and valproic acid on bone mineral density, IGF-I and IGFBP-3. *J Pediatr Endocrinol Metab* 2006;19:529–534.
10. Mintzer S, Boppana P, Toguri J, DeSantis A. Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006;47:510–515.
11. Babayigit A, Dirik E, Bober E, Cakmakci H. Adverse effects of antiepileptic drugs on bone mineral density. *Pediatr Neurol* 2006;35:177–181.