

## DO NEW ANTIEPILEPTIC DRUGS INTERACT WITH ORAL CONTRACEPTIVES?

### Effect of Topiramate or Carbamazepine on the Pharmacokinetics of an Oral Contraceptive Containing Norethindrone and Ethinyl Estradiol in Healthy Obese and Nonobese Female Subjects

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**PURPOSE:** To study the pharmacokinetics of a combination oral contraceptive (OC) containing norethindrone and ethinyl estradiol during OC monotherapy, concomitant OC and topiramate (TPM) therapy, and concomitant OC and carbamazepine (CBZ) therapy to evaluate comparatively the pharmacokinetic interaction, which may cause contraceptive failure.

**METHODS:** This randomized, open-label, five-group study included two 28-day cycles. Five groups of female subjects received oral doses of ORTHO-NOVUM 1/35 alone (cycle 1) and then concomitant with TPM or CBZ (cycle 2). The treatment groups were group 1, TPM, 50 mg/day; group 2, TPM, 100 mg/day; group 3, TPM, 200 mg/day; group 4, TPM, 200 mg/day (obese women); and group 5, CBZ, 600 mg/day. Group 4 comprised obese women whose body mass index (BMI) was between 30 and 35 kg/m<sup>2</sup>. The BMI of the remaining four groups was 27 kg/m<sup>2</sup>.

**RESULTS:** Coadministration of TPM at daily doses of 50, 100, and 200 mg (nonobese) and 200 mg (obese) nonsignificantly ( $P > .05$ ) changed the mean area under the curve (AUC) of ethinyl estradiol by -12%, +5%, -11%, and -9%, respectively, compared with OC monotherapy. A similar nonsignificant difference was observed with the plasma levels and AUC values of norethindrone ( $P > .05$ ). CBZ (600 mg/day) significantly ( $P < .05$ ) decreased the AUC values of norethindrone and ethinyl estradiol by 58% and 42%, respectively, and increased their respective oral clearance by 69% and 127% ( $P < .05$ ). Because CBZ induces CYP3A-mediated and glucuronide conjugation metabolic pathways, the significant increase in

the oral clearance of ethinyl estradiol and norethindrone was anticipated.

**CONCLUSIONS:** TPM, at daily doses of 50 to 200 mg, does not interact with an OC containing norethindrone and ethinyl estradiol. The lack of the TPM-OC interaction is notable when it is compared with the CBZ-OC interaction.

### COMMENTARY

The effect of antiepileptic drug (AED) administration on the pharmacokinetics and efficacy of medications that patients take concomitantly is important to understand to anticipate and correct for changes in bioavailability and, therefore, efficacy. Although older AEDs [e.g., phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ)] have clearly been recognized to be inducers of the hepatic P450 (CYP)3A metabolic system, the new generation of AEDs has not been extensively studied in this regard. Women with epilepsy or with nonepileptic conditions, which have responded therapeutically to AEDs (e.g., neuropathic pain, bipolar disorder, migraine prophylaxis), are frequently treated with oral contraceptive medications containing norethindrone and ethinyl estradiol, both of which are metabolized in the P450 (CYP)3A system. The current recommendation is to treat women with the lowest dose of hormone possible to avoid systemic complications. Thus AEDs that reduce the hormonal concentration result in even lower than anticipated hormonal effects and risk contraceptive failure.

This study rigorously evaluated five groups of women who served as their own controls when they were not receiving AED treatment with topiramate (TPM) or CBZ. The investigators also evaluated the change in the 6 $\beta$ -hydroxycortisol-to-cortisol ratio, which is a marker for CYP3A induction. Women were evaluated in a study unit for accurate collection of blood samples for pharmacokinetic assessment. As expected, the CBZ group showed significant effect on peak plasma concentration ( $C_{max}$ ) and mean area under the curve (AUC) for both norethindrone ( $C_{max}$  decreased by 37%, and AUC, by 19%) and ethinyl estradiol ( $C_{max}$  decreased by 58%, and AUC, 42%). TPM effects were not significant in nonobese and obese women at any of the TPM doses. The milligram-per-kilogram dose at 200 mg/day



was lower in the obese subjects who had body mass index (BMI) between 31 and 35 kg/m<sup>2</sup> compared with the nonobese subjects with a BMI of 27 kg/m<sup>2</sup> or less. The induction was not significant in any of the TPM groups, as reflected in the 6 $\beta$ -hydroxycortisol-to-cortisol ratios, compared with the baseline condition.

TPM doses in monotherapy are typically 200 mg/day or less. This study would confirm that failure of oral contracep-

tives during TPM treatment, by using doses of 200 mg/day or less, is thus not likely for reasons other than noncompliance. Neurologists, gynecologists, and primary care physicians who treat these women should be cognizant that low-dose hormonal therapy can be used in women receiving TPM monotherapy.

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