

## LEVETIRACETAM AND ORAL CONTRACEPTIVES

### Levetiracetam Does Not Alter the Pharmacokinetics of an Oral Contraceptive in Healthy Women

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**PURPOSE:** This study was designed to evaluate whether levetiracetam (LEV), a novel antiepileptic drug (AED), influences the pharmacokinetics of steroid oral contraceptives.

**METHODS:** During a run-in phase, 18 healthy female patients received an oral contraceptive containing ethinyl estradiol, 0.03 mg, and levonorgestrel, 0.15 mg, for the first 21 days of two consecutive menstrual cycles. In a subsequent double-blind, randomized, two-way crossover treatment phase, subjects received either LEV, 500 mg, or placebo twice daily concomitant with the oral contraceptive. Plasma concentrations of ethinyl estradiol and levonorgestrel were measured on days 14 and 15 of the two treatment periods for the evaluation of the 24-h kinetic parameters, and an additional sample was collected on day 21 to determine the trough plasma concentrations. Serum progesterone and luteinizing hormone (LH) levels were determined on days 13, 14, 15, and 21 of each cycle of the treatment phase.

**RESULTS:** The plasma concentration–time curves and pharmacokinetic parameters of ethinyl estradiol and levonorgestrel were not statistically different during concomitant treatment with either LEV or placebo. The ratios of the log-transformed geometric mean areas under the plasma concentration–time curves (AUCs), maximal ( $C_{max}$ ) and minimal ( $C_{min}$ ) plasma concentrations, and trough concentrations on day 21 ( $C_{21}$ ) ranged from 99.12 to 99.96% for ethinyl estradiol and from 97.13 to 99.41% for levonorgestrel. The 90% confidence intervals of these ratios were well within the 80 to 125% acceptance range for lack of interaction. Serum progesterone and LH concentrations were fairly constant during the run-in and treatment phases and remained markedly below their respective physiologic levels. Safety

and menstrual-bleeding patterns were comparable during LEV and placebo administration.

**CONCLUSIONS:** LEV does not affect the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and levonorgestrel, and on the basis of serum progesterone and LH levels, it does not affect the contraceptive efficacy.

### COMMENTARY

Female patients with epilepsy who are of childbearing age have specific concerns about the antiepileptic drugs (AEDs) their neurologists choose to use in their treatment plan. One of these is whether the AED interacts with other medication. Many of these young women are taking hormonal contraception, and frequently the “mini-pill” is chosen by the gynecologist wishing to minimize hormonal side effects. Many AEDs do induce the P450 system and reduce the contraceptive steroid levels, resulting in potential “pill failure.” Levetiracetam (LEV) does not have liver P450–dependent metabolism and has not induced cytochrome P450 enzyme systems (CYP) activity *in vitro* in rat hepatocytes.

Twenty-two women receiving oral contraception with 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel were treated for two cycles, one with LEV and one with placebo in a double-blind, placebo-controlled, two-way crossover design. LEV doses were 500 mg every 12 h. Trough levels of ethinyl estradiol and levonorgestrel were determined on day 21; serum progesterone and luteinizing hormone (LH) levels were determined on days 13, 14, 15, and 21. The data were reported on 18 subjects. Pharmacokinetics of the hormonal treatment were unchanged with LEV treatment compared with placebo. Progesterone and LH peaks were suppressed, and breakthrough bleeding was not seen during LEV administration.

This well-designed study confirms that LEV can confidently be given to women who have had proven efficacy on the “mini-pill” for oral contraception without loss of efficacy or interference in the pill’s pharmacokinetics. The neurologist must still consider the effects of other comedications that the patient is taking but can be reassured that the addition of LEV will not compromise the efficacy of the patient’s birth control.

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