Oral Contraceptives and Reduced Lamotrigine Efficacy

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For most reported drug interactions involving oral contraceptives (OCs), the OC is the drug affected by the interaction (ie, the "object drug"). For example, enzyme inducers such as rifampin enhance the metabolism of OCs, thus increasing the risk of contraceptive failure and unintended pregnancy.

Some data suggest that OCs can affect the metabolism of drugs metabolized by cytochrome P450 (CYP) 1A2 or CYP3A4 and possibly other enzymes, but the interactions are generally not considered of high clinical importance.[1] The ability of OCs to reduce lamotrigine plasma concentrations and efficacy, however, is well documented and probably of substantial clinical importance.

WHAT DATA SUPPORT THE INTERACTION?

Over a decade ago, a report described 7 patients who developed a mean 49% decrease in lamotrigine plasma concentrations with concurrent use of OCs.[2] Some patients developed reduced seizure control following OC use.

In a later study by the same group, lamotrigine plasma concentrations were compared in 22 women taking lamotrigine with a combined OC (ethinyl estradiol plus a progestogen) and 30 women taking lamotrigine without OCs. The mean steady state lamotrigine concentration in those taking OCs was less than half that seen in the women not taking OCs.[3]

Several subsequent studies have confirmed that lamotrigine plasma concentrations are substantially lower in women taking combined OCs (ethinyl estradiol plus a progestogen) than in those not taking an OC.[4-7] In most studies, women taking OCs have lamotrigine plasma concentrations approximately 40% to 50% lower than those not taking OCs. In one study, it took about 8 days after starting the OC for the maximal decrease in lamotrigine levels.

There is convincing clinical evidence that combined OCs containing ethinyl estradiol can substantially reduce lamotrigine plasma concentrations, thus increasing the risk of seizures.

Although most of the studies of this interaction were short-term and involved relatively small numbers of patients (approximately 20 to 50), reductions in lamotrigine plasma concentrations have been consistently found. Moreover, the magnitude of the interaction is such that one should expect reduced lamotrigine efficacy with an increased risk of seizures in at least some patients.

The clinical evidence suggests that lamotrigine levels may increase during the "pill-free" week when the OC is temporarily discontinued.[7] Accordingly, if lamotrigine dosage has been increased to compensate for the OC interaction, stopping the OC may result in lamotrigine adverse effects, as has been reported in some patients.[2]

WHAT IS THE MECHANISM?

Lamotrigine clearance is substantially higher in patients taking OCs, probably due to the ability of the estrogenic component of the OC (ethinyl estradiol) to induce the hepatic glucuronidation of lamotrigine. Other evidence suggests that OCs can enhance glucuronidation of concurrently administered drugs.

DO PROGESTOGEN-ONLY OCS INTERACT?

Women receiving progestogen-only contraceptives (oral, topical, or parenteral) did not have lower lamotrigine serum concentrations in one study.[4] The number of patients studied was small, however, so more research is needed to establish whether progestogen-only contraception interacts with lamotrigine.

SUMMARY

There is convincing clinical evidence that combined OCs containing ethinyl estradiol can substantially reduce lamotrigine plasma concentrations, thus increasing the risk of seizures.

If OCs are added to lamotrigine therapy, it would be prudent to monitor lamotrigine plasma levels before and after starting the OC. Adjustments in lamotrigine dose may be necessary. One should also consider the possibility that a change in the estrogen content of an OC may result in changes in lamotrigine plasma concentrations.

Overall, it would appear that, with careful monitoring, one can safely combine lamotrigine and OCs, but in selected patients it may be preferable to avoid the combination.

Preliminary evidence suggests that, unlike ethinyl estradiol, progestogens do not interact with lamotrigine, so using progestogen-only contraception may prove to be a method of avoiding the interaction. Nonhormonal methods of contraception may also be used to avoid the interaction if necessary. ***PT***

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