Short Communication

An Ethinyl Estradiol-Levonorgestrel Containing Oral Contraceptive Does Not Alter Cytochrome P4502C9 In Vivo Activity

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ABSTRACT

Oral contraceptives have been in wide use for more than 50 years. Levonorgestrel, a commonly employed progestin component of combined oral contraceptives, was implicated in drug-drug interaction mediated via CYP2C9. Although in vitro studies refuted this interaction, there are no confirmatory in vivo studies. In the current study, we examined the phenotypic status of CYP2C9 using low-dose (125 mg) tolbutamide before and after oral contraceptive use in reproductive age women. Blood was collected 24 hours after the tolbutamide oral dose was administered, plasma was isolated, and tolbutamide concentration (C24) was measured using liquid chromatography–mass spectrometry. The natural logarithm of tolbutamide C24, a metric for CYP2C9 phenotype, was found to be equivalent (within 80–125% equivalency boundaries) before and after oral contraceptive use. In conclusion, levonorgestrel-containing oral contraceptives, the most commonly used form of oral contraception, do not affect the status of the CYP2C9 enzyme. This suggests that it is safe to coadminister levonorgestrel-containing oral contraceptives and CYP2C9 substrates, which include a wide array of drugs.

ABBREVIATIONS: LNG, levonorgestrel; OC, oral contraceptive; P450, cytochrome P450.
29.1 ± 4.6 years, with a mean body mass index of 39.7 ± 6.8 kg/m². Five of the study participants were *1/*2 allele expressors, one participant was a *1/*3 expressor, and the rest were homozygous wild-type expressors.

CYP2C9 status was unchanged after 3 weeks of OC use (Fig. 1). The median predose tolbutamide C24 was 1538 ng/ml (range, 469, 6331), and the median postdose C24 was 1446 ng/ml (range, 485, 6294). The geometric mean of the differences in C24 before and after OC use was 0.9978 (90% confidence interval, 0.9781–1.0174). The confidence interval is well within the acceptable equivalency boundaries of 80%–125% recommended by regulatory agencies (US Food and Drug Administration, 2003; European Medicines Agency, 2010). This study is consistent with the lack of change in CYP2C9 status reported by Gainer (2003) using in vitro systems. However, Sandberg et al. (2004) observed significantly lower CYP2C9 activity in women taking OCs compared with women naïve to OC treatment. Interestingly, the type of progestin was not recorded in their study; hence, it can be speculated that the different progestins have different effects on CYP2C9 activity. The above speculation is supported by the findings of a study in which triphasic OCs containing norgestimate as a source of progestin were shown to enhance the activity of CYP2C9 (Shelepova et al., 2005).

Ethinyl estradiol, the estrogenic component of the OC regimen, was shown to inhibit various P450 isozymes, including CYP2C9 (Laine et al., 2003; Chang et al., 2009). Both of these in vitro studies demonstrate that CYP2C9 inhibition occurs at a supra-micromolar concentration of ethinyl estradiol. The maximum plasma concentrations of ethinyl estradiol achieved by women in the current study were approximately 100 pg/ml (approximately 0.33 pM) (Edelman et al., 2013). Given the 10⁶–10⁹ differential in the plasma concentrations and IC₅₀, it is highly unlikely that ethinyl estradiol contributes to CYP2C9 variability among women who use OCs.

We previously demonstrated that OC use suppresses CYP3A4 activity in women (Edelman et al., 2012). In the current study, we observed a lack of effect of OCs on CYP2C9 activity, suggesting that OCs have isozyme-specific effects. Studies, including ours, further suggest that the type of progestin influences the overall effect of OCs on P450 enzyme status in women. In conclusion, LNG-containing OCs, the most commonly used form of OC, does not affect the status of the CYP2C9 enzyme. This suggests that it is safe to coadminister LNG-containing OCs and CYP2C9 substrates, which include a wide array of drugs.

**Fig. 1.** OC use and CYP2C9 clearance. (A) Each box represents 25th to 75th percentile data with median (solid line) and mean (broken line), and whiskers depicting 5th to 95th percentile data (N = 34). (B) Each of the 34 subjects was depicted with their respective predose and postdose CYP2C9 clearance surrogate marker.

Ganesh Cherala, Jacob Pearson, Cheryl Maslen, Alison Edelman

**Authorship Contributions**

Participated in research design: Cherala, Edelman.
Conducted experiments: Cherala, Pearson, Edelman.
Contributed new reagents or analytic tools: Maslen.
Performed data analysis: Pearson, Cherala.
Wrote or contributed to the writing of the manuscript: Cherala, Pearson, Edelman.
References


