Letter to the Editor

IS 17α-ETHINYL ESTRADIOL AN INHIBITOR OF CYTOCHROME P450 2C19?

We have read with great interest the increasing number of publications reporting that oral contraceptive (OC) formulations can decrease CYP2C19 activity. For example, Palovaara et al. (2003) evaluated the effect of two OC formulations on the hydroxylation of omeprazole. One formulation contained EE (40 μg) and LNG (60 μg), whereas the second contained LNG (60 μg) and was devoid of EE. The combination of EE and LNG increased both the area under the plasma concentration vs. time curve of omeprazole (38%) and the omeprazole to 5-hydroxy omeprazole area under the plasma concentration vs. time curve ratio (48%). LNG alone had no affect on the PK and metabolism of omeprazole. In addition, neither formulation inhibited CYP3A4-catalyzed omeprazole sulfone formation. Because the hydroxylation of omeprazole is widely accepted as an index of CYP2C19 activity (Chang et al., 1995; Lasker et al., 1998; Abelo et al., 2000; Kita et al., 2001), the authors concluded that OC preparations containing EE decrease CYP2C19 activity. The observations of Palovaara et al. (2003) confirm the findings of Laine et al. (2000), who also reported an increase (~100%) in the omeprazole to 5-hydroxy omeprazole ratio in plasma. In the same study, the ratio of (S)-mephenytoin to (R)-mephenytoin in urine (S/R ratio) increased from 0.11 to 0.28, and the effect was similar to that observed with subjects genotyped CYP2C19*1/1 (versus CYP2C19*1/1). A comparable change in the S/R ratio has been reported by Hagg et al. (2001) and Tamminga et al. (1999).

EE-containing OC formulations have also been shown to affect the PK and metabolism of diazepam, propranolol, proguanil, and selegiline (Abernethy et al., 1982; Walle et al., 1996; Laine et al., 1999; McGready et al., 2003). All four drugs are reported to be CYP2C19 substrates. However, the effect of EE on their PK cannot be ascribed to CYP2C19 alone, because other cytochromes P450 are involved in metabolism (Jung et al., 1997; Yang et al., 1999; McGinnity et al., 2000; Hidestrand et al., 2001). The same cannot be said for the urinary mephenytoin S/R ratio and the omeprazole to 5-hydroxy omeprazole ratio in plasma. Both have served as a useful index of CYP2C19 activity and have been validated with genotyped subjects (Rodrigues and Rushmore, 2002).

Although the results of these various clinical drug interaction studies are compelling, it cannot be assumed that EE is a clinically relevant inhibitor of CYP2C19. The dose of EE is low (30–50 μg), and peak plasma concentrations (total EE) range between 0.6 and 0.7 nM (Belle et al., 2002). Moreover, Jurima et al. (1985) have reported that EE itself is a weak inhibitor (Ki ~100 μM) of human liver microsomal mephenytoin (racemate) hydroxylase activity, whereas Laine et al. (2003) observed inhibition (70%) of omeprazole 5-hydroxylation only at a high concentration of EE (0.1 mM). We have also determined that EE is a relatively weak, reversible inhibitor (IC50 ~19 μM) of CYP2C19 (4'-hydroxylation of (S)-mephenytoin) in human liver microsomes. The IC50 was determined at the Km of (S)-mephenytoin (80 μM; substrate concentration/Km ~1.0) and (R)-N-3-benzyl-phenobarbital (IC50 = 0.3 μM) served as a positive control. Therefore, these data imply that the concentration of inhibitor/Ki for EE is very low.

EE has been shown to be a mechanism-based inhibitor (Ki, 18 μM; kinauc, 0.04 min−1) of CYP3A4 in vitro (Lin et al., 2002). In our hands, up to 70% inhibition of testosterone 6β-hydroxylase activity was observed when EE (50 μM) was preincubated (30 min) with NADPH-foated human liver microsomes. In contrast, preincubation of EE (0.1 to 50 μM) with human liver microsomes resulted in no inhibition of (S)-mephenytoin 4'-hydroxylase activity. Ticlopidine (10 μM), on the other hand, behaved as a preincubation time-dependent inhibitor (50% inhibition) and also served as a positive control (Taiteshi et al., 1999; Ko et al., 2000; Ha-Duong et al., 2001). Based on our preliminary data, therefore, the kinauc/Ki ratio of EE for CYP2C19 is probably lower than that for CYP3A4 (0.002 min−1 · μM−1). It is worth noting that despite overt mechanism-based inhibition of CYP3A4 in vitro, EE has a modest effect on the PK and metabolism of midazolam, a sensitive CYP3A4 probe drug (Palovaara et al., 2000; Belle et al., 2002; Lin et al., 2002). The in vitro study described herein was expanded to include a number of EE metabolites (e.g., EE 3-O-sulfate, EE 3-0-glucuronide, and 2-methoxy EE), and none were shown to be inhibitors of human liver microsomal (S)-mephenytoin 4'-hydroxylase activity.

At first glance, it is difficult to conclude that the effect of OCs on CYP2C19 activity is due to inhibition (reversible or mechanism-based) of the enzyme by EE. Further studies are needed to elucidate the mechanism of interaction involving omeprazole and mephenyton. Toward this end, it will be important to evaluate carefully the estrogenic and progestogenic components of OC formulations and their metabolites, as reversible and mechanism-based inhibitors of CYP2C19 in vitro. In turn, in vitro-in vivo correlations can be attempted. Such studies are important because it has been estimated that up to 70 million women worldwide take OC formulations (Belle et al., 2002), and relatively little mechanistic information is available concerning the effects of these formulations on cytochromes P450.

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References

1 Abbreviations used are: OC, oral contraceptive; EE, 17α-ethinyl estradiol; LNG, levonorgestrel; PK, pharmacokinetics; S/R ratio, ratio of (S)-mephenytoin to (R)-mephenytoin in urine.

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Sundberg M (2001) CYP2B6 and CYP2C19 as the major enzymes responsible for the metabolism of selegiline, a drug used in the treatment of Parkinson’s disease, as revealed from experiments with recombinant enzymes. Drug Metab Dispos 29:1480–1484.


