Up-regulation of Cytochrome P450 2C19 by 17-alpha Hydroxyprogesterone Caproate in Primary Cultures of Human Hepatocytes

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Purpose
The 17-alpha hydroxyprogesterone caproate (17-OHPC) is commonly prescribed for the prevention of recurrent, spontaneous preterm birth in women with singleton gestations from week 16 until 36. The 17-OHPC is known to be metabolized by CYP3A enzyme. Given that patients on 17-OHPC may be on other medications that are also metabolized by CYP enzymes, it is important to understand the potential impact of 17-OHPC on the activity of various CYP enzymes in the liver.

Methods
Primary human hepatocytes from four donors were treated with vehicle or 17-OHPC for 72 hours, followed by 1-hour incubation of a validated CYP cocktail of phenacetin (CYP1A2), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6) and testosterone (CYP3A4/5). The gene expression of these P450 enzymes was examined by qRT-PCR. The activities of these P450 enzymes in primary human hepatocytes were measured by quantitating the metabolites derived from each of the above substrates using liquid chromatography-tandem mass spectrometry.

Results
The results showed that in primary human hepatocytes, 17-OHPC at 1 µM increased CYP2C19 expression to 2.4-fold (P<0.001) and CYP2C19 activity to 2.8-fold (P<0.01), compared with that in vehicle-treated cells. This induction seemed to be in a concentration-dependent manner. In addition, a strong positive correlation was observed between the expression and activity of CYP2C19 (r=0.9, P<0.001). No significant induction on the expression and activities of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 was observed in primary human hepatocytes treated with 17-OHPC.

Conclusion
Our results suggest that 17-OHPC may selectively alter the expression and activity of certain CYP enzymes and may alter the pharmacokinetics of certain co-administered drugs.