Buprenorphine Metabolism in Human Liver, Human Placenta, and Recombinant Cyp19 Microsomes

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Background and Hypothesis:

Buprenorphine (BUP), a partial opioid agonist, is commonly used to treat opioid use disorder in pregnant women. BUP is metabolized in the liver by cytochrome P450s (CYP) and UDP-Glucuronosyltransferases (UGT). Compared to non-pregnant women, higher doses of BUP are needed during pregnancy to maintain therapeutic concentrations. We hypothesize that the placenta has a role in the metabolism of BUP, thus contributing to the need for higher doses during pregnancy.

Experimental Design or Project Methods: :

BUP was incubated with human liver microsome (HLM), human placenta microsome (HPM) or recombinant CYP19 microsome (rCYP19). Norbuprenorphine (Nor-BUP) formation was measured by HPLC/MS/MS (Thermo TSQ Quantum Ultra). Positive controls included midazolam for HLMs and testosterone for HPMs and rCYP19, and negative controls were without NADPH. Initial experiments assessed linearity with time and protein concentration. Subsequently, BUP concentrations were varied and Nor-BUP formation vs. BUP concentration was fitted to the Michaelis–Menten equation (GraphPad Prism) to calculate K_m and V_{max}.

Results:

The K_m was 11.89 μM and V_{max} was 0.4627 μmol/min/mg for Nor-BUP formation following incubation of BUP (0-20 μM) with HLM. Higher concentrations of BUP indicated non-typical Michaelis–Menten kinetics. Results from the HPM show metabolism of BUP to Nor-BUP is present in the placenta. Incubation of BUP in rCYP19, an enzyme known to be in human placenta, resulted in Nor-BUP formation, indicating its role in BUP metabolism.

Conclusions and Potential Impact: :

The K_m and V_{max} values generated from concentrations of 5-20 μM in HLM is comparable with existing data. Because multiple enzymes breakdown BUP with different K_m and V_{max} values, a curve not adhering to the normal Michaelis–Menten shape over 20 μM BUP is reasonable in HLMs. Formation of Nor-BUP following incubation of BUP in rCYP19 and HPMs suggest their role in the metabolism of BUP in pregnant women.

Understanding the role of placenta in metabolizing BUP will provide insight to fetal drug exposure. Placental metabolism of BUP would possibly indicate lower exposure to BUP but higher exposure to nor-BUP to the fetus. Future directions of this study will quantify placental metabolism of BUP, investigate other pathways of BUP metabolism in the placenta, and determine drug interactions that may exacerbate Neonatal Abstinence Syndrome when co-administered with BUP.