Metabolic Kinetics of Bupropion in Human Liver and Intestinal Subcellular Fractions
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Purpose
Bupropion is a clinically available drug product used for depression. Generics of Wellbutrin extended release (XL) were approved based on bioequivalence (BE) studies comparing the 150mg strength of the products to Wellbutrin XL 150mg. The results were extrapolated to establish bioequivalence of the 300mg product. However, BE studies for 300mg XL showed bioinequivalence for some generics. One possible factor may be the lack of understanding the metabolism of bupropion, particularly relating to liver and intestinal metabolism. Hydroxybupropion and threohydrobupropion/erythrohydrobupropion are the active primary metabolites of bupropion (25-50% of bupropion activity) by the enzymes CYP450 2B6 and Carbonyl Reductase respectively. The purpose of this study was to understand the metabolite formation in vitro using liver and intestinal microsome and S9 fractions.

Methods
Liver and intestinal microsome and S9 stability experiments were conducted using concentrations of bupropion from 1-4000μM. NADPH (20mM) was used for the cofactor and to initiate the reaction. Sample was collected at time points from 0-90 minutes, and the reaction was terminated by spiking the sample in methanol containing the internal standard (venlafaxine) at 160nM. All samples were quantified by LC-MS/MS and the method was validated for specificity, matrix effect, and linearity.

Results
In these studies, we found that hydroxybupropion was formed in the liver but was not detected in microsome and S9 fraction of intestines. The estimated Vmax was 131±5.8 and 51±1.9 pmol/min/mg and the Km was 87.9±20.2 and 99.5±18.9μM for the liver microsome and S9 fractions, respectively. For the diastereomer, threohydrobupropion was the dominant metabolite in both the liver and intestines. For the liver microsome and S9 fractions, threohydrobupropion was formed at a Vmax of 98.37±6.6 and 99±7.58 pmol/min/mg and the Km 186.3±53.48 and 265±77.79μM respectively. In the intestines, threohydrobupropion was formed at a lesser extent in both microsome and S9, the Vmax was 5.5±0.3 and 25.87±2.8 pmol/min/mg and the Km 149.9±28.86 and 573.4±88.9 μM respectively. Erythohydrobupropion was not detectable in either microsome or S9 of intestines.

Conclusion
The metabolism of bupropion in vitro shows that the liver and intestines have distinct metabolite profiles of bupropion. These differences in metabolism might provide evidence towards the understanding of bioinequivalence of bupropion products.