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Brian D. Chapron

Kansas City Children's Mercy, bchapron@cmh.edu

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# Characterization of the Relative Contribution of CYP2D6 and CYP3A4 to the Metabolism of Pimozide

**Submitting/Presenting Author (must be a trainee):** Brian Chapron

**Primary Email Address:** bchapron@cmh.edu

Resident/Psychology Intern

Fellow

**Primary Mentor (one name only):** J. Steven Leeder

**Other authors/contributors involved in project:** Jean Dinh

**IRB Number:**

**Describe role of Submitting/Presenting Trainee in this project (limit 150 words):**

Assisted in experimental design, conducted *in vitro* experiments, and performed data analysis.

**Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words**

**Background:**

Tourette syndrome (TS) is a neuropsychiatric disorder that affects approximately 1% of children in the United States. Pimozide is one of only two drugs that hold an FDA-approved indication for the treatment of TS. However, clinical use of pimozide remains limited due to exposure-dependent associations with QTc prolongation. Initial clinical and preclinical data demonstrated hepatic CYP3A4-mediated metabolism to 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one (DHPBI) was the major route for systemic pimozide clearance. However, a more recent small scale population pharmacokinetic study implicated CYP2D6 as a major pathway for pimozide clearance. Because CYP2D6 activity is greatly affected by genetic polymorphisms, the FDA amended the pimozide package insert to include CYP2D6 pharmacogenomics-based dosing guidelines for both adults and children. These revised dosing guidelines rely upon assumptions that were either untested or in conflict with the prior observations regarding primarily CYP3A4-mediated metabolism of pimozide *in vitro*.

**Objectives/Goal:**

In light of changes in the pimozide dosing guidelines and the drug's narrow therapeutic index, it is crucial to reconcile contrasting results from the initial studies and more recent investigations of pimozide metabolism. The goal of our work is to employ established *in vitro* methodologies to ascertain accurate enzymatic parameters for pimozide metabolism.

## **Methods/Design:**

We revisited the previous characterization of pimozide metabolism in human liver microsomes and recombinant human P450s; this time under clinically-relevant concentrations. The use of clinically-relevant substrate concentrations are crucial because use of excessively high concentrations has the potential to substantially underestimate the relative contribution of relatively high-affinity low-capacity enzymes to overall metabolism; this may have occurred in the previous *in vitro* experiments and lead to the aforementioned discrepancies in the data.

## **Results:**

Two novel metabolites of pimozide, 5- and 6-hydroxypimozide, were identified and demonstrated to be produced primarily by CYP2D6 with a relatively minor contribution from CYP3A4. The putative major metabolite of pimozide, DHPBI, was confirmed to be produced primarily by CYP3A4 with a small but detectable contribution from CYP3A5 and CYP3A7. The previously identified “minor” CYP1A2-mediated pathway for DHPBI formation was not observed in our experiments, nor was CYP2D6-mediated formation observed. Analysis of theoretical maximal drug-drug interactions across a range of CYP3A4 and CYP2D6 expression levels was also evaluated with the majority of patients being demonstrated to be incapable of experiencing even a weak drug-drug interaction via the CYP2D6 pathway.

## **Conclusions:**

Metabolism of pimozide can be catalyzed by CYP2D6 and results in the formation of relatively specific hydroxypimozide metabolites. The relatively bespoke nature of the formation of DHPBI for CYP3A4 and 5-/6-hydroxypimozide for CYP2D6 also suggest the metabolite to metabolite ratios from initial doses may be useful for forecasting doses suitable during chronic administration. In the near future, we plan to incorporate our parameter estimates into a physiologically-based pharmacokinetic model (PBPK)-based decision support tool to help clinicians select the appropriate dose of pimozide to achieve a standardized drug exposure and also to define an individual’s unique propensity for drug-drug interactions that could alter circulating pimozide concentrations.