Single Dose Pharmacokinetics of Atomoxetine in Children with ADHD Stratified by Their CYP2D6 Activity Score

JT Brown1, SM Abdel-Rahman2, L van Haandel3, A Gaedigk2, and JS Leeder2

1University of Minnesota College of Pharmacy, Duluth, MN, 2Children’s Mercy Hospitals and Clinics, Kansas City, MO, USA

Introduction

Atomoxetine is a norepinephrine reuptake inhibitor commonly utilized in pediatric attention deficit/hyperactivity disorder (ADHD), and is metabolized primarily by the highly polymorphic drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6) to the active metabolite 4-hydroxyatomoxetine (4-OH-ATX). Subsequently, 4-OH-ATX is rapidly glucuronidated to an inactive metabolite. In vitro studies of atomoxetine indicate that CYP2D6 is the predominant CYP catalyzing the formation of 4-OH-ATX, the major oxidative metabolite, and intrinsic clearance towards atomoxetine is dramatically (>50-fold) reduced in hepatic microsomes from CYP2D6 poor metabolizers. Additionally, the N-desmethylatomoxetine metabolite is formed via the CYP2C19 pathway. A pharmacokinetic study in adults revealed that atomoxetine’s half-life was four-fold longer in CYP2D6 poor metabolizers (approximately 20 hours) as compared to extensive metabolizers (approximately 5 hours), and that 4-hydroxylation (followed by glucuronidation) was the major route of elimination. The objective of this study was to determine the magnitude of effect of CYP2D6 genotype on atomoxetine, 4-OH-ATX, and N-desmethylatomoxetine on systemic exposure in children and adolescents with ADHD.

Methods

Patient population: 23 participants between the ages of 6 to 17 years were selected based upon a diagnosis of ADHD and their inclusion in a prior study in which CYP2D6 genotypes and phenotypes (via single-dose dextromethorphan) were determined.

Study design: This was an open label, single-dose pharmacokinetic study of atomoxetine in participants with varying degrees of CYP2D6 activity. Of the 23 participants included in the data analysis, it had a CYP2D6 activity score of 2 or more (EM2), it had a CYP2D6 activity score of 1 (EM1), 3 had a CYP2D6 activity score of 0.5 (IM), and 4 had a CYP2D6 activity of 0 (PM). Of note, 3 of the 4 participants in the PM group were siblings. Prior to dosing, participants underwent a physical exam, an electrocardiogram, vital signs, a complete blood count, basic metabolic panel, and urinalysis, all of which were interpreted and approved by a physician. All participants less than 70 kg were dosed at or near 0.5 mg/kg, while all participants greater than 70 kg were given a maximum of 40 mg. Participants completed the study with an overnight stay within the pediatric clinical research unit. Plasma samples, as well as heart rate and blood pressure, were obtained at or near 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours. For participants with a CYP2D6 activity score of 0, 48 and 72-hour levels were also collected due to an expected extended half-life. All urine was collected throughout the pharmacokinetic sampling timeframe.

CYP2D6 Genotyping: Subjects were genotyped to allow the detection of 2*2, 3*3, 4*4, 5*5, 6*6, 7*7, 8*8, 9*9, 10, 11, 12, 13*, 17*, 23, 29, 32, 38, 39*4, 40*, 41*, 42, and 45*4. Determination of plasma drug concentrations: Analysis was conducted by UPLC-MS/MS.

Safety: Adverse events were recorded on the case report form, and were defined as any undesirable sign, symptom, or medical condition occurring after the informed consent/assent form was signed.

Statistical methods: Atomoxetine pharmacokinetic data for each CYP2D6 activity group was examined using standard descriptive statistics. Analysis of variance was utilized for direct comparisons of pharmacokinetic parameters between the four different CYP2D6 activity score groups.

Results

Summary and Discussion

1. Compared to those with a CYP2D6 activity score of 1 or more, children with CYP2D6 activity scores of 0 or 0.5 prescribed equivalent weight-based doses and experienced ~10- and ~3.5-fold greater overall exposure to atomoxetine, respectively.

2. Given the extensive variability in systemic exposure with weight-based dosing, individualized dosing to achieve a target exposure will be necessary to investigate the role of genetic variation in the drug target and downstream effector pathways to optimize clinical effectiveness and minimize adverse events.

Acknowledgment: 1 R01 HD058556-05: “Exogenous and Endogenous Biomarkers of CYP2D6 Variability in Pediatrics” from NICHD.

*P < 0.05 vs. CYP2D6 AS 0