INTRODUCTION

The metabolism of standard atypical antipsychotics [e.g., risperidone, olanzapine, aripiprazole, quetiapine, clozapine, brexpiprazole, and paliperidone] involves CYP3A4. Most treatments involve significant plasma drug concentration changes when co-administered with CYP3A4 inhibitors or inducers. Such interactions are of clinical concern as schizophrenia patient take concomitant medications interacting with CYP3A4 leading to dose adjustment to ensure treatment efficacy, safety, and tolerability.

Briloxazine is a serotonin-dopamine modulator displaying a high affinity for D2/3 (and 5HT2A receptors) and a moderate affinity for the serotonin transporter [SERT]3-5. This agent rapidly achieved steady-state safety and pharmacokinetic profile based on its phase I and 2 clinical experience.6-8 It possesses differentiated pharmacological and safety profiles over other antipsychotics. Currently, briloxazine is prescribed in phase 3 development for schizophrenia9.

Preclinical in vitro work identified CYP3A4 as the primary enzyme involved in briloxazine’s metabolism.10 Due to the potential for drug-drug interaction via this pathway, the need exists to evaluate the extent of potential drug-drug interaction between briloxazine with a strong CYP3A4 inhibitor (itraconazole) and inducer (phenytoin) to provide clinicians with dosing guidance when using this new treatment.

OBJECTIVE AND METHODS

Objective

The objective involved comparing briloxazine’s pharmacokinetic (PK) parameters (Cmax, AUC0-t, and AUC0-∞) after a single 15 mg oral dose tablet on 1) Day 1 alone, 2) Day 17 with steady-state itraconazole (a strong CYP3A4 inhibitor), and 3) Day 27 steady-state phenytoin (a strong CYP3A4 inducer).

Methods

This study involved a single-center, two-part, open-label, fluid-sequence, drug-drug interaction design. Part A (Figure 1) evaluated the effects of steady state itraconazole (200 mg QD) on the PK of a single oral 15 mg dose of briloxazine in 13 subjects. Subjects took a single oral briloxazine 15 mg dose and all medications with a light breakfast after at least 10 hours fasting.

Part B (Figure 2) assessed the effect of phenytoin (200 mg TID) dosed in a steady state on the single oral dose of briloxazine in 17 subjects. Subjects took a single oral briloxazine 15 mg dose and all medications fasting (at least 10 hours).

RESULTS

Pharmacokinetics

Mean (± SD) Briloxazine Concentration-Time Profiles (Part A)

Table 1 illustrates the statistical comparison following the administration of briloxazine single oral dose (15 mg) alone or in combination with multiple oral doses of itraconazole (200 mg QD).

DISCUSSION

This two-part study provided useful insight into the PK profile of briloxazine when co-administered with itraconazole [a strong CYP3A4 inhibitor] and phenytoin (a strong CYP3A4 inducer).

**CONCLUSION**

Briloxazine [a strong CYP3A4 inducer] did not affect itraconazole’s PK. Accordingly, briloxazine may be co-administered with itraconazole and other strong CYP3A4 inducers. This profile presents a useful addition to the clinical management of schizophrenia to minimize the clinical risk associated with drug-drug interactions seen with other antipsychotics, particularly with CYP3A inhibitors.

REFERENCES

| 17. Laxminarayan Bhat, Seema R Bhat, and Arulprakash Ramakrishnan, and Padaliappan Kulanthaivel

DISCLOSURES & ACKNOWLEDGEMENTS

Laxminarayan Bhat, Seema R Bhat, and Arulprakash Ramakrishnan are employees, and Pulaliappan Kulanthaivel is a consultant of Reviva Pharmaceuticals Holdings Inc.