CYP3A Inhibition and Induction Exert Limited Effects on Brilaroxazine Pharmacokinetics

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INTRODUCTION

The metabolism of standard of care antipsychotics (e.g., aripiprazole, lurasidone, risperidone, quetiapine, cariprazine, brexpiprazole, and clozapine) involves CYP3A4[1-6]. Most treatments realize significant plasma drug concentration changes when co-administered with CYP3A4 inhibitors or inducers[1-6]. Such interactions are of clinical concern as schizophrenia patients take concomitant medications interacting with CYP3A4, leading to dose adjustment to ensure treatment efficacy, safety, and tolerability[1-7].

Brilaroxazine is a serotonin-dopamine modulator displaying a high affinity for $D_{2/3/4}$ and 5-$HT_{2A/2B/7}$ receptors and a moderate affinity for the serotonin transporter (SERT)[8-10]. This agent brings an established efficacy, safety, and pharmacokinetic profile based on its phase 1 and 2 clinical experience[8-15]. It possesses differentiated pharmacological and safety profiles over other antipsychotics. Currently, brilaroxazine is proceeding in phase 3 development for schizophrenia[16].

Preclinical *in vitro* work identified CYP3A4 as the primary enzyme involved in brilaroxazine's metabolism[17]. Due to the potential for drug-drug interaction via this pathway, the need exists to evaluate the extent of potential drug-drug interaction between brilaroxazine with a strong CYP3A4 inhibitor (itraconazole) and inducer (phenytoin) to provide clinicians with dosing guidance when using this new treatment in practice[6].

OBJECTIVE AND METHODS

Objective

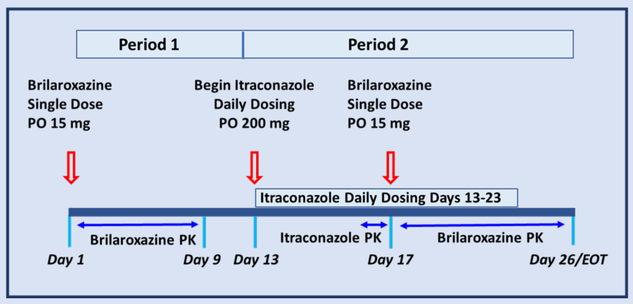
The objective involved comparing brilaroxazine's pharmacokinetic (PK) parameters (Cmax, AUC0-∞, and AUC0-t) after a single 15 mg oral dose tablet on 1) Day 1 alone, 2) Day 17 with steady-state itraconazole (a strong CYP3A4 inhibitor), and 3) Day 27 steady-state phenytoin (a strong CYP3A4 inducer)[6].

Methods

This study involved a single-center, two-part, open-label, fixed-sequence, drug-drug interaction design[6].

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 brilaroxazine in 13 subjects. Subjects took a single oral brilaroxazine 15 mg dose and all medications with a light breakfast after at least 10 hours fasting.

FIGURE 1

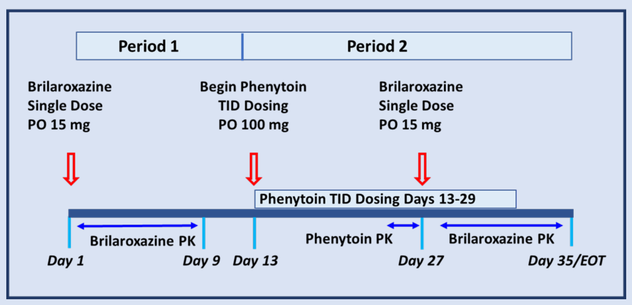


Brilaroxazine blood samples on Days 1-10 and Days 17-26 occurred at Time 0 (pre-dose), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144-, 168-, 192-, and 216-hours post-dose (total: 38 samples/subject).

Measurement of itraconazole concentrations occurred within 10 minutes before its dosing on Days 15, 16, 18 and 19, and on Day 17 at time 0 (pre-dose) and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose (total: 11 samples/subject).

Part B (Figure 2) assessed the effect of phenytoin (100 mg TID) dosed to a steady state on the single-dose PK of brilaroxazine in 17 subjects. Subjects took a single oral brilaroxazine 15 mg dose and all medications fasting (at least 10 hours).

FIGURE 2



Brilaroxazine blood samples on Days 1-9 and Days 27-35 occurred at Time 0 (pre-dose) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120-, 144-, 168-, and 192-hours post-dose (total: 36 samples/subject). On Day 27, the pre-dose PK sample was collected within ~10 minutes before dosing to coincide with the pre-dose phenytoin PK sample.

Phenytoin blood samples occurred on Days 25, 26, and 27 before the 8:00 a.m. dose (within 10 minutes before dosing). Day 26 included samples at 1, 2, 3, 4, 5 and 6 hours after the morning dose, with the 6-hour post-dose sample before the 2nd phenytoin dose.

Subjects: Eligible healthy individuals, 18-55 years, who were nonsmoking adult males or females, provided written informed consent and complied with all study provisions. The body mass index range was 18- 32 kg/m^2, and the body weight was ≥50 kg. Females needed a negative pregnancy test on Days -1 and 12. For Part A, they had to use a medically acceptable method of birth control during the study and for 4 weeks after the end of the study visit or be surgically sterile or postmenopausal. For Part B, female subjects had to be of non-childbearing potential and surgically sterile or postmenopausal. Male subjects need to use a highly effective method of contraception from Day -1 until 12 weeks post-study.

Study exclusions included a clinically significant history or presence of gastrointestinal, cardiovascular, musculoskeletal, endocrine, hematologic, psychiatric, renal, hepatic, bronchopulmonary, neurologic, immunologic, lipid metabolism disorders, or drug hypersensitivity as determined by the Investigator. Part B exclusions entailed Asian descent, prior history of acute hepatotoxicity due to phenytoin, history or presence of porphyria, clinically significant risk of suicidality, presence or relevant history of organic brain disorders, or history of severe and/or serious dermatologic reactions to phenytoin or any other medication.

Bioanalysis: The study used validated LC-MS/MS assay methods to determine the plasma concentrations of brilaroxazine, RP5081, itraconazole, and phenytoin.

Pharmacokinetic Analysis: Determining brilaroxazine and metabolite (RP5081) C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ involved WinNonlin version 8.1 (Certara, Princeton, NJ), using non-compartmental methods involved log transformation and a linear mixed-effects model with treatment as a fixed effect and subject as a random effect. The analysis involved calculating the geometric least squares mean for each treatment, the ratio of the geometric least squares means, and their 90% confidence intervals (CIs).

RESULTS

FIGURE 3

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

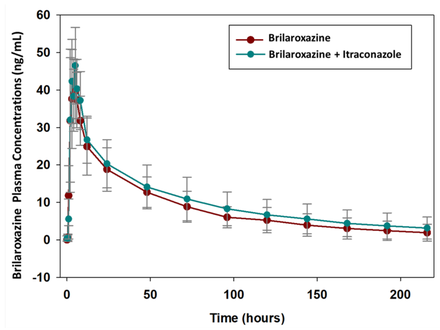


Figure 3 displays the plasma concentration-time profiles, following the administration of brilaroxazine single oral dose (15 mg) alone or in combination with multiple oral doses of itraconazole (200 mg QD).

TABLE 1

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

	Least Squares Geometric Means				Ratio of Geometric Means (%)	Ratio of Geometric Means 90% CI (%)	Intra-Subject CV%
PK Parameter	n	Brilaroxazine 15 mg	n	Brilaroxazine 15 mg + Itraconazole 200 mg	[Brilaroxazine 15 mg + Itraconazole 200 mg] / RP5063 15 mg	[Brilaroxazine 15 mg + Itraconazole 200 mg] / Brilaroxazine 15 mg	
C_{max} (ng/mL)	10	45.12	10	48.51	107.52	[98.98, 116.79]	10.11
AUC_{0-t} (h*ng/mL)	10	1770	10	2034	114.94	[105.94, 124.72]	9.981
$AUC_{0-\infty}$ (h*ng/mL)	9	1965	8	2215	112.74	[102.66, 123.81]	9.082

CI = confidence interval; CV% = percent coefficient of variation.

Geometric mean is the mean back-transformed from the mean of logarithmic values to the original scale. Least squares means are derived from a mixed model with terms for Treatment as a fixed effect and Subject as a random effect. The intra-subject CV% is the coefficient of variation based on the model defined as the sqrt(e^$sigma^2$ - 1) * 100, $sigma^2$ is the within-subject variance of log-scale data. n is the number of subjects with the corresponding non-missing PK parameters in both treatments.

FIGURE 4

Mean (± SD) Brilaroxazine Concentration – Time Profiles (Part B)

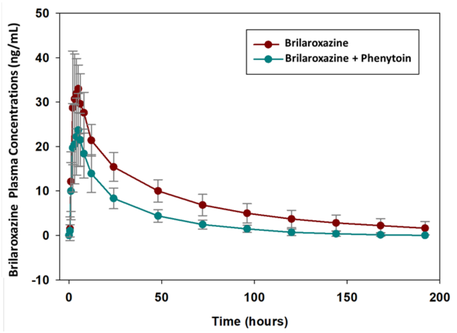


Figure 4 displays the plasma concentration-time profiles following the administration of brilaroxazine single oral dose (15 mg) alone or in combination with multiple oral doses of phenytoin (100 mg TID), respectively.

TABLE 2

Table 2 illustrates the statistical comparison following the administration of brilaroxazine single oral dose (15 mg) alone or in combination with multiple oral doses of phenytoin (100 mg TID), respectively.

	Least Squares Geometric Means				Ratio of Geometric Means (%)	Ratio of Geometric Means 90% CI (%)	
PK Parameter	n	Brilaroxazine 15 mg	n	Brilaroxazine 15 mg + Phenytoin ER 100 mg TID	[Brilaroxazine 15 mg + Phenytoin ER 100 mg TID] / RP5063 15 mg	[Brilaroxazine 15 mg + Phenytoin ER 100 mg TID] / RP5063 15 mg	Intra-Subject CV%
C_{max} (ng/mL)	17	37.28	17	25.15	67.46	[59.20, 76.87]	22.08
AUC_{0-t} (h*ng/mL)	17	1395	17	606	43.42	[38.11, 49.46]	22.04
$AUC_{0-\infty}$ (h*ng/mL)	16	1477	17	677	45.87	[41.98, 50.11]	14.41

CI = confidence interval; CV% = percent coefficient of variation. NC = Not calculable.

Geometric mean is the mean back-transformed from the mean of logarithmic values to the original scale. Least squares means are derived from a mixed model with terms for Treatment as a fixed effect and Subject as a random effect. The intra-subject CV% is the coefficient of variation based on the model defined as the sqrt(e^$sigma^2$ - 1) * 100, $sigma^2$ is the within-subject variance of log-scale data. n is the number of subjects with the corresponding non-missing PK parameters in both treatments.

DISCUSSION

This two-part study provided useful insight into the PK profile of brilaroxazine when co-administered with itraconazole (a strong CYP3A inhibitor) and phenytoin (a strong CYP3A inducer).

Part A: Single brilaroxazine dose co-administered with itraconazole at steady-state resulted in a slight increase of 8, 15 and 13% in brilaroxazine Cmax, AUC0-t, and AUC0-∞, respectively (90% CI within no effect boundaries of 80-125%). No notable difference in brilaroxazine's mean elimination half-life existed between the drug administered alone and concomitantly with itraconazole. These findings suggest that the drug-drug interaction between itraconazole and brilaroxazine is not clinically significant.

Brilaroxazine metabolite (RP5081) showed Cmax and AUC0-t decreases of ~35% and ~22%, respectively, with brilaroxazine dose co-administered with itraconazole. The associated 90% CIs fell below the lower boundary of 80% for both PK parameters. Given the relatively low levels of the RP5081 metabolite present in plasma in proportion to the parent compound brilaroxazine (i.e., mean RP5081 Cmax is ~7% of mean brilaroxazine Cmax on a nanomolar basis in the absence of itraconazole) and the moderate effect on RP5081 Cmax and AUC0-t, this effect on the metabolite's PK parameters is not likely to be clinically significant.

Part B: Single brilaroxazine dose co-administered with phenytoin at steady-state resulted in brilaroxazine Cmax, AUC0-t, and AUC0∞ decreases of ~33%, 57% and 54%, respectively. The associated 90% CIs were below the lower boundary of 80% for all 3 PK parameters. Brilaroxazine metabolite RP5081 showed Cmax and AUC0-t increases of ~53% and ~8%, respectively. These findings suggest a potentially clinically significant drug-drug interaction between phenytoin (a strong CYP3A inducer) and brilaroxazine.

Significance: Brilaroxazine may be used concomitantly with other medications metabolized via CYP3A4. Polypharmacy is a common practice in treating schizophrenia as they suffer from multiple health issues and most patients with schizophrenia are reported to take over 5 concomitant medications[18]. Drug-drug interactions alter plasma drug concentrations and can impact a drug's efficacy and side effect profiles. Approximately 50% of prescribed drugs and over 25% of approved antipsychotics are known to cause drug interactions in the presence of a strong CYP3A4 inhibitor drug[19,20]. These data indicate that brilaroxazine possesses a smaller relative change (than current commercially available antipsychotic medications) in drug exposure (AUC) when it is used with medications that either inhibit or induce CYP3A4 (Figure 5).

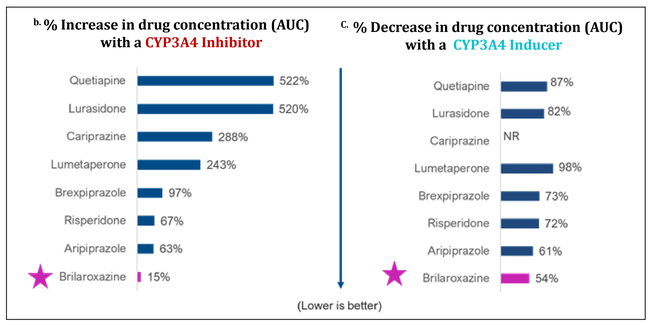
These findings can guide clinicians concerning the dosing of brilaroxazine in practice. No dose adjustment appears to be necessary for patients on itraconazole or other concomitant treatments with strong CPY3A4 inhibitors. Alternatively, brilaroxazine dose adjustment in some clinical settings may require when used with phenytoin. Thus, for patients on concurrent treatments that are strong CYP3A4 inducers, some brilaroxazine dose adjustments may be needed to maintain therapeutic benefit.

FIGURE 5

Decreased Potential for Drug-Drug Interactions with Brilaroxazine Relative to Current Antipsychotic Medications with CPY3A4 Inhibitors (a,b) or Inducers (c)[21-30]

a.

Change in drug concentration with a CYP3A4 Inhibitor	
Antipsychotic	Fold increase vs brilaroxazine
Brilaroxazine	--
Aripiprazole	4.2x
Risperidone	4.5x
Brexpiprazole	6.5x
Lumetaperone	16.2x
Cariprazine	19.2x
Lurasidone	34.7x
Quetiapine	34.8x



*Olanzapine[9] not evaluated; metabolized by CYP1A2[31]; NR: Not reported.

CONCLUSION

Itraconazole (a strong CYP3A4 inhibitor) did not affect brilaroxazine's PK. Accordingly, brilaroxazine may be co-administered with itraconazole and other strong CYP3A inhibitors. Phenytoin (a strong CYP3A4 inducer) decreased brilaroxazine exposure by approximately 50%. Thus, brilaroxazine dose modification may be needed when co-administering with phenytoin and other strong CYP3A inducers. This profile presents a useful addition to the clinical management of schizophrenia to minimize the clinical risks associated with drug-drug interactions seen with other antipsychotics, particularly with CYP3A inhibitors.

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DISCLOSURES & ACKNOWLEDGEMENTS

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