Single-Dose Brilaroxazine Pharmacokinetics, Metabolism, and Excretion Profile in Animals and Humans

Laxminarayan Bhat, Seema R Bhat, and Palaniappan Kulanthaivel

Reviva Pharmaceuticals Holdings, Inc., Cupertino, California, USA (19925 Stevens Creek Blvd, Ste 100, Cupertino, CA 95014)

Poster#579

INTRODUCTION

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)[1-3]. This agent brings an established efficacy, safety, and pharmacokinetic profile based on its phase 1 and 2 clinical experience[1-8]. It possesses differentiated pharmacological and safety profiles over other antipsychotics[1-8]. Currently, brilaroxazine is proceeding through phase 3 development for schizophrenia[9].

Previous works have defined the pharmacokinetic (PK) profile via single ascending doses (SAD) in normal healthy volunteers[1], multiple ascending doses in patients with stable schizophrenia[1], and pharmacokinetic modeling based on phase 2 study data from individuals with acute schizophrenia or schizoaffective disorder[2]. These findings indicate that brilaroxazine offers a predictable pharmacokinetic profile with daily doses up to 100 mg and would allow for once daily dosing[1,2].

Still, the need exists to provide a fuller picture of the PK, Metabolism, and Excretion (PME) profiles of brilaroxazine. A particular interest is to compare the single-dose PME profiles in animals and humans.

OBJECTIVE

This research describes the PME profiles associated with a single oral dose of [^{14}C]-brilaroxazine in separate studies involving mice, canines, and humans.

METHODS

Regulatory

Animal studies occurred at an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) facility and in compliance with Institutional Animal Care and Use Committees (IACUC) protocols. The human study had investigational review board approval. All studies US Nuclear Regulatory Commission (NRC), and the State Bureau of Radiation Protection regulations (New Jersey and Pennsylvania).

Procedures

The Mice study engaged 42 adult male CD-1 mice (Charles River, Raleigh, NC) in two separate groups to evaluate a single oral 10 mg/kg (~400 µCi/kg) dose of [^{14}C]brilaroxazine. Group 1 (PK) involved 27 animals/divided into 9 separate subgroups (3 per) for blood/plasma collection at pre-dose, 0.25, 0.5, 1, 2, 6, 24, 48, and 72 hours post-dose. Group 2 (Mass balance) comprised 15 animals in three separate metabolisms cages (5 per) to collect urine, feces, and cage rinses at pre-dose, 0-8, 8-24, (0-24 for feces), 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours.

The Canine Study engaged 3 three naïve male beagle dogs (Charles River Laboratories, Mattawan, MI) housed in separate cages to evaluate a single oral 10 mg/kg (~75 µCi/kg) dose of [^{14}C]brilaroxazine. Sample collection included: 1) Blood/Plasma at Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 hours post-dose; 2) Urine at Pre-dose, 0-8, 8-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours post-dose; 3) Feces at Pre-dose, 0-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours post-dose; 4) Emesis at 0.5 hours post brilaroxazine dosing; 4) Cage rinse at Pre-dose, 0-24, 24-48, 48-72, 72-96, 96-120- and 120-144 hours post-dose; and 5) Cage wipe at 144 hours.

The Human Study involved six healthy male human subjects in evaluating a single oral 15 mg (~163 µCi) dose of [^{14}C]brilaroxazine. Samples included: 1) Blood at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, and 432 hours post-dose (up to 28 samples per subject); 2) Plasma at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, and 432 hours post-dose (additional plasma samples at 1, 4, 8, 24, 48 and 72 hours post-dose for metabolite identification); 3) Urine at Pre-dose, 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-36 hours, 36-48 hours, 48-72 hours, 72-96 hours, 96-120 hours, 120-144 hours, 144-168 hours, 168-192 hours, 192-216 hours, 216-240 hours, 240-264 hours, 264-288 hours, 288-312 hours, 312-336 hours, 336-360 hours, 360-384 hours, 384-408 hours, 408-432 hours, and 432-456 hours; 4) Feces at Pre-dose, 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, 96-120 hours, 120-144 hours, 144-168 hours, 168-192 hours, 192-216 hours, 216-240 hours, 240-264 hours, 264-288 hours, 288-312 hours, 312-336 hours, 336-360 hours, 360-384 hours, 384-408 hours, and 408-432 hours; and 5) Urine container rinse and fecal wipes.

Analysis

Radioactivity concentration of brilaroxazine and its metabolites in blood, plasma and excreta samples utilized liquid scintillation counting (LSC) or a combination of combustion with LSC. Plasma concentration determination of unlabeled brilaroxazine and its metabolites used a validated liquid chromatography/tandem mass spectrometry method. Identification of brilaroxazine-related metabolite structures in biological samples involved mass spectral analysis or via direct comparison with authentic standards. Calculating plasma pharmacokinetic parameters of total radioactivity and brilaroxazine employed non-compartmental analysis (WinNonlin Software, Certara, Princeton, NJ).

RESULTS

FIGURE 1

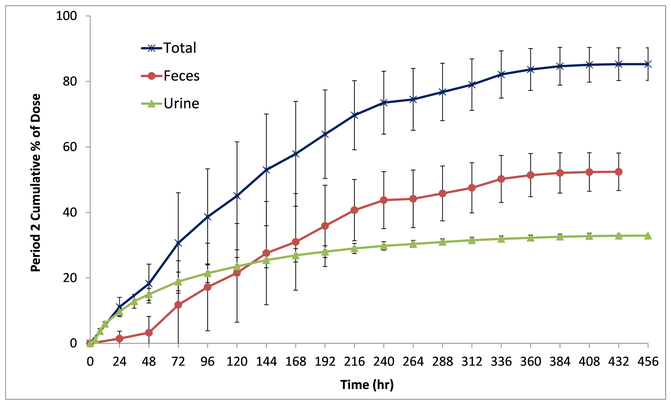

Figure 1 presents the recovery of radioactivity as a percentage of the administered dose in humans. The cumulative total was 86.1%. Feces represented the predominant route (53.3%), and urine was the secondary path (32.8%).

The animal data reflected a similar split. Feces represented the predominant recovery route of the administered dose for mice (77.9%) and canines (55.3%). Urine recovery was the secondary route for mice (10.3%) and canines (15.0%), both lower than in humans.

FIGURE 2

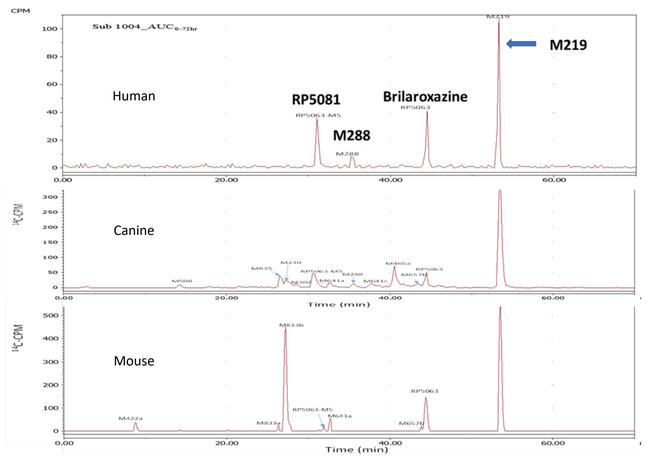

Figure 2 shows the profile of brilaroxazine and metabolites in plasma. Brilaroxazine accounted for approximately 12%, 7%, and 12% of the total circulating radioactivity exposure in mice, canines, and humans, respectively. A fragment of brilaroxazine, N-(2,3-chlorophenyl)glycine (M219), was the major circulating metabolite in all species. It accounted for approximately 53.5%, 51.2% and 40.5% of the total radioactivity exposure in mice, canines, and humans, respectively.

TABLE 1

Parent/Metabolite	% $AUC_{0\text{-}72}$ hr Human	% $AUC_{0\text{-}24}$ hr Mice	%$AUC_{0\text{-}24}$ hr Canines
Brilaroxazine	28.9	12.0	6.9
RP5081	20.1	1.5	8.9
M288	6.9	ND	2.2
M219	40.5	53.5	51.2

Table 1 displays the cumulation of parent brilaroxazine and its metabolites RP5081, M288, and M219. All metabolites, except for M288 in mice, were present across species.

Human plasma had no unique human-specific metabolite. All metabolites in human plasma were found in either mice or canines.

FIGURE 3

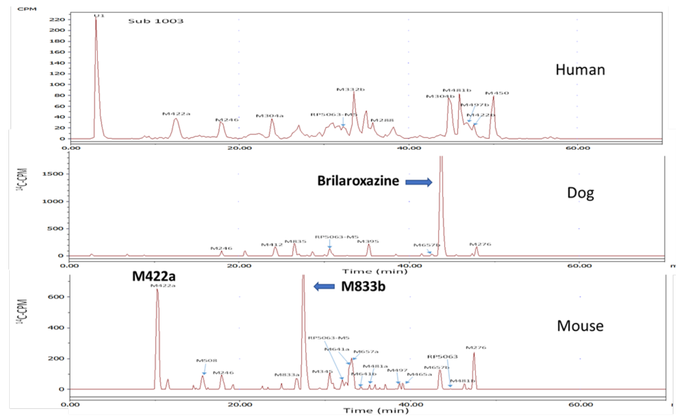

Figure 3 depicts the renal elimination profile of radioactive brilaroxazine and its metabolites. Mice and humans excreted brilaroxazine in trace amounts via the renal route. In contrast, it was the major metabolite detected in the urine of canines. Mice had significant excretion of M422a and 833b metabolites.

FIGURE 4

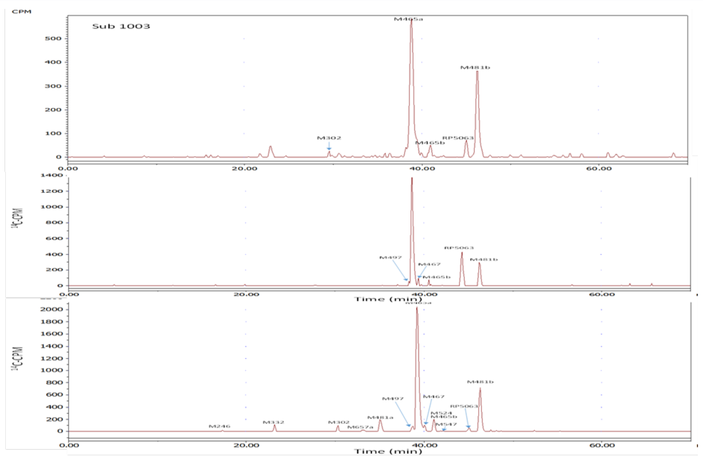

Figure 4 offers a closer view of excreted metabolites. Like other observations, no unique human metabolite existed unique from either mice or canines. Mono-hydroxylated brilaroxazine (M465a) was the excreted metabolite identified with the highest radioactivity seen in all species. M481b (Parent+20) was most significant in mice and humans, and brilaroxazine in canines.

FIGURE 5

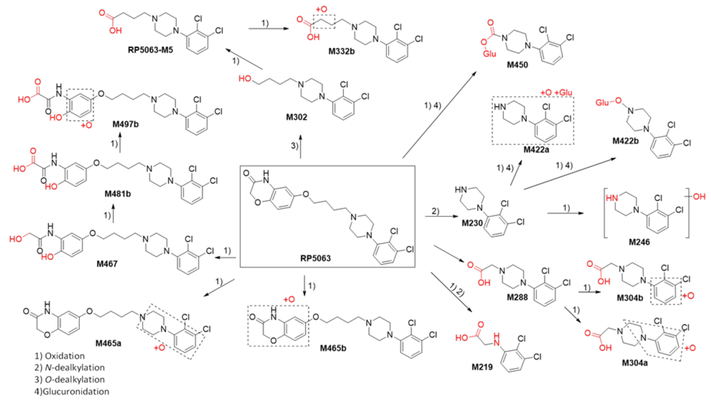

Figure 5 maps the representation of metabolic pathways for brilaroxazine in humans. Oxidation, N- or O-dealkylation with subsequent sulfation and/or conjugation with glucuronic acid appeared as the metabolic pathways of brilaroxazine in tested species.

DISCUSSION

This poster presents the PME profiles based on a single oral dose of [^{14}C]-brilaroxazine in mice, canines, and humans. Following a single oral dose of [^{14}C]brilaroxazine, mice had the highest total recovery at 88.2%, then humans at 86.1%, and finally, canines at 77.8%. Differences could be due to group numbers, sample collection extensiveness, and canine emesis. The parent drug and metabolites were predominantly recovered in the feces of all species. Some variations did appear between humans with the latter having high fecal and lower renal excretion percentages.

The major circulating metabolite in all species was the same (M219). M465a predominated in fecal excretion. The most notable observation was that no human-specific metabolite was detected in plasma, and the major metabolite in excreta of all species was the mono-hydroxylated metabolite M465a.

Finally, common metabolic pathways emerge from this work, involving oxidation, N- or O-dealkylation with subsequent sulfation and/or conjugation with glucuronic acid.

CONCLUSION

The single oral dose [^{14}C]-brilaroxazine PME profile is similar among all three species. Feces represent the predominant route of excretion. M219 is the major circulating metabolite and M465a is the major excreted metabolite; no human-specific metabolite appears to exist in plasma. The emergent metabolic pathways for all species involve oxidation, N- or O-dealkylation with subsequent sulfation and/or conjugation with glucuronic acid.

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DISCLOSURES & ACKNOWLEDGMENTS

Disclosures: Laxminarayan Bhat, Seema R Bhat, are employees, and Palaniappan Kulanthaivel is a consultant of Reviva Pharmaceutical Holdings, Inc

Acknowledgments: John M. York, PharmD, MBA, Akita Biomedical, Inc. provided editorial support, and Reviva Pharmaceutical Holdings, Inc. funded this effort.