INTRODUCTION

Brilaroxazine is a serotonin-dopamine modulator displaying a high affinity for D2/D3/D4 and 5-HT2A/2B/7 receptors and a moderate affinity for the serotonin transporter (SERT)\(^1\). This agent brings an established efficacy, safety, and pharmacokinetic profile based on its phase 1 and 2 clinical experiences\(^2\). It possesses differentiated pharmacological and safety profiles over other antipsychotics\(^3\). Currently, brilaroxazine is proceeding through phase 3 development for schizophrenia\(^4\).

Previous works have defined the pharmacokinetic (PK) profile via single ascending doses (SAD) in healthy volunteers\(^5\), multiple ascending doses in patients with stable schizophrenia, and pharmacokinetic modeling based on phase 2 study data in patients 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\(^6\).

Still, the need to explore a wider picture of the PK, Metabolism, and Excretion (PME) profile of brilaroxazine is particularly important to compare the single-dose PKE profiles in animals and humans.

OBJECTIVE

This research describes the PKM 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 institutional review board approval. All studies US Nuclear Regulatory Commission (NRC), and the State Bureau of Radiation Protection regulations (New Jersey and Pennsylvania).

Procedures

The Mouse Study engaged 42 adult male CD-1 mice (Charles River, Raleigh, NC) in two separate groups to evaluate a single oral \(10 \text{ mg/kg} (\sim 400 \mu\text{g/kg})\) dose of \(^{14}C\)-brilaroxazine. Group 1 (PK) involved 27 animals divided into nine separate subgroups (3 per block) plasma collection at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose. Group 2 (Mass Balance) comprised 15 animals in three separate metabolism cages (5 per group) to collect urine, feces, and cage rinses at pre-dose, 0, 0.5, 0.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-dose.

The Canine Study engaged 3 three naive male beagle dogs (Charles River Laboratories, Munich, Germany) housed in separate cages to evaluate a single oral \(10 \text{ mg/kg} (\sim 25 \mu\text{g/kg})\) dose of \(^{14}C\)-brilaroxazine. Example collection included: 1) Blood/Plasma at Pre-dose, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, and 144 hours post-dose; 2) Urine at Pre-dose, 0-24, 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 from 0.5 hours post brilaroxazine dosing; 5) 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 post-dose.

The Human Study involved six healthy male human subjects in evaluating \(10 \text{ mg/kg} (\sim 400 \mu\text{g/kg})\) dose of \(^{14}C\)-brilaroxazine. Group 1 (PK) involved 6 subjects divided into 3 subgroups (2 per block) at pre-dose, 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-dose.

RESULTS

The single oral dose \(^{14}C\)-brilaroxazine PME profile is similar among all three species. Focus represents 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 emerging metabolic pathways for all species involve 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 PKM 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 the highest fecal and lower oral excretion percentages.

The major circulating metabolite in all species was the M219. M465a predominated in fecal excretion of all species. Some variations did appear between humans with the latter having the highest fecal and lower oral excretion percentages.

The major circulating metabolite in all species was the 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 animal data reflected a similar split. Focus represented the predominant recovery route of the administered dose for mice (77.9%) and canines (55.1%). Urine recovery was the secondary route for mice (10.3%) and canines (15.0%), both lower than in humans.

REFERENCES


DISCLOSURES & ACKNOWLEDGMENTS

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