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Absorption, Metabolism, and Excretion of Brilaroxazine in Rats

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Background: Brilaroxazine, a novel multimodal neuromodulator, belongs to a class of next-generation treatments for schizophrenia and comorbid conditions. It functions as a $D_{2/3/4}$ and 5-$HT_{1A/2A}$ partial agonist and a 5 $HT_{2B/7}$ antagonist with binding affinity for 5-$HT_{2B} > D_2$. It also mediates inflammatory cytokines. With defined efficacy, safety, and pharmacokinetics from clinical trials, it offers a differentiated profile over other antipsychotics.

Brilaroxazine's development involved rats, mice, and dogs for nonclinical toxicological evaluations. This study evaluated the absorption, metabolism, and excretion of brilaroxazine in rats after a single ^{14}C-brilaroxazine dose to qualify rats as a suitable toxicology species.

Methods: This study involved 12 male Sprague Dawley rats divided equally into three groups. These animals received a single [^{14}C]-brilaroxazine 20 mg/kg (200 mCi/kg) oral dose. Group 1 rats had a bile-duct cannula (BDC) surgically implanted for bile and feces collection. Group 2 rats had blood collected for metabolite evaluation. Group 3 rats had urine and feces collected to determine the mass balance. Maximal post-dose collection times for bile samples were 72 hours (Group 1), serial blood samples were 72 hours (Group 2), and urine and feces samples were 168 hours (Group 3).

Sample analysis included liquid scintillation counting (LSC) or a combustion/ LSC combination (blood, plasma, and excreta), validated liquid chromatography–mass spectrometry/mass spectrometry (unlabeled brilaroxazine and RP5081 plasma concentrations), and mass spectral analysis or direct comparison with authentic standards for metabolite structures (brilaroxazine, and metabolite RP5081).

Results: Bile or feces of BDC rats or intact rats were the predominant routes for dose radioactivity excretion. The percent of the administered dose recovered in Group 1 BDC rat bile, feces, and urine accounted for 79.52%, 13.02%, and 5.60%, respectively. Bile and urine in Group 3 intact rats showed at least 85% dose absorption, with 81.51% of the administered dose recovered in feces and 8.89% in urine.

Brilaroxazine represented ∼31% of the circulating radioactivity exposure with three primary metabolites- M641a (oxidation + glucuronidation), RP5081 (O-dealkylated acid), and M219 (N-[2,3-dichlorphenyl]-glycine)- accounting for ∼29%,∼16%, and ∼16%, respectively. In Group 1 rat bile, the analysis did not detect brilaroxazine but identified M641a, accounting for 70% of the bile radioactivity or 56% of the dose. In Group 3 intact rat feces, the mono-hydroxylated compound, M465a, was the major metabolite, accounting for 86% of the fecal radioactivity or 71% of the dose. The gut microflora likely converted the glucuronide metabolite, M641a, observed in Group 1 rat bile, to the mono-hydroxylated metabolite M465a, which underwent fecal elimination in Group 3 rats. Glucuronidase hydrolysis of M641a, producing M465a in a near quantitative yield, confirmed this supposition.

Conclusions: Following oral administration, brilaroxazine in rats underwent rapid absorption, extensive metabolism, and elimination via hepato-biliary excretion. The primary human metabolites, RP5081 and M219, were among the most commonly circulated in rats. Both humans and rats utilize 465a formation as the major metabolic pathway. These findings confirm that rats are a suitable rodent species for the toxicological evaluations of brilaroxazine.

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