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Metabolism and Pharmacokinetics of the Acyclovir Prodrug BW 256U87 in Cynomolgus Monkeys. P. de Miranda and T. C. Burnette. Burroughs Wellcome Co., Research Triangle Park, NC 27709, USA

BW 256U87, the L-valyl ester of acyclovir (ACV, ZOVIRAX®), demonstrated good oral absorption and nearly complete conversion to ACV in Cynomolgus monkeys, indicating its suitability as an orally administered prodrug. The major urinary metabolites of [8-^{14}C]BW 256U87, administered orally (10 and 25 mg/kg) or intravenously (10 mg/kg) to male monkeys, were ACV (50 to 60% of urinary radioactivity), 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine (8-hydroxy-ACV) (25 to 30%), and 9-carboxymethoxymethylguanine (CMMG) (11 to 12%). Following oral or intravenous dosing, intact prodrug accounted for only 0.5% or 6% of urinary radioactivity, respectively. Dose-independent kinetics were observed for ACV derived from orally administered [8-^{14}C]BW 256U87 at the 10 and 25 mg/kg dose levels, with both AUC (24 μM·hr and 60 μM·hr, respectively) and C_{max} (8 μM and 23 μM, respectively) increasing nearly in proportion to the dose. ACV was present in plasma at all sampling times (5 min to 7 hr post-dose) after both oral doses, while the prodrug was not detected following either oral dose. The elimination of ACV was monophasic with an apparent half-life of 1.5 hr. Similar to ACV, both 8-hydroxy-ACV and CMMG demonstrated dose-independent kinetics with apparent elimination half-lives of 1 to 1.5 hr. Intravenously administered [8-^{14}C]BW 256U87 (10 mg/kg) was rapidly converted to ACV, with the elimination half-life of ACV (0.9 hr) being 1.5-fold that of the prodrug (0.6 hr). The oral bioavailability of ACV derived from BW 256U87 in Cynomolgus monkeys was 67 ± 13%, representing a significant improvement over the poor bioavailability of ACV itself in primates.