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Metabolic Disposition of BW 256U87, the L-Valyl Ester of Acyclovir, in the Rat. T. C. Burnette and P. de Miranda. Burroughs Wellcome Co., Research Triangle Park, NC 27709, USA

In disposition studies in male CD rats, the prodrug BW 256U87 demonstrated good oral absorption, rapid distribution and elimination, and extensive biotransformation to acyclovir (ACV, ZOVIRAX®). The mean urinary excretion of radioactivity following administration of [8-^{14}C]BW 256U87 (25 mg/kg) was 65% of an oral dose and 95% of an intravenous dose. ACV was the predominant radiolabeled urinary metabolite in the rat accounting for 57% or 65% of an oral or intravenous dose, respectively. Radioactivity from an oral dose of [8-^{14}C]BW 256U87 (10 mg/kg) was distributed to all fourteen tissues examined, by 20 min post-dose. Tissues that received the highest exposure to radioactivity were the stomach, small intestine, kidney, liver, lymph nodes, and skin. Only the brain had a significantly lower exposure than plasma. Radioactivity in most tissues cleared by 24 hr post-dose and that in urine and feces accounted for essentially all of the administered dose (99%) by 48 hr post-dose. ACV derived from BW 256U87 administered orally or intravenously exhibited dose-independent pharmacokinetics at 10 and 25 mg/kg. The observed mean C_{max} (5 μM and 13 μM, respectively) and mean AUC's (7 μM·hr and 18 μM·hr, respectively) for ACV, achieved with orally administered prodrug, were at least 4-fold higher than those achieved with equivalent doses of ACV. The half-life of ACV derived from BW 256U87 was approximately 1 hr, while that of the prodrug itself was only 6 to 8 min. Based on the ratio (ACV to BW 256U87) of AUC's, prodrug administered orally was more efficiently metabolized than that administered intravenously, indicating first-pass intestinal and hepatic effects. Rapid *in vitro* hydrolysis of BW 256U87 in homogenates of both intestine and liver from rats further indicated the significance of presystemic metabolism. This hydrolytic activity in subcellular fractions of rat tissue homogenates has been investigated in initial steps toward isolation and characterization of the enzyme(s) which enable(s) BW 256U87 to be an effective oral prodrug for ACV.

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Amino Acid Esters of Acyclovir as Oral Prodrugs. L. Beauchamp, G.F. Orr, P. de Miranda, T. Burnette, T.A. Krenitsky, Burroughs Wellcome Co., 3030 Cornwallis Rd., RTP, N. C. 27709,U.S.A.

Eighteen amino acid esters of the antiherpetic drug, acyclovir, were synthesized as potential prodrugs for oral administration. Their efficiencies as prodrugs were evaluated in rats by measuring the urinary recovery of acyclovir. Ten prodrugs produced greater amounts of the parent drug in the urine. The L-amino acid esters were better prodrugs than the corresponding D- or D,L-isomers, suggesting the involvement of a stereoselective transporter. The L-valyl ester, 256U87, was the best prodrug. Since 256U87 was stable in aqueous solutions, its conversion to acyclovir *in vivo* was probably enzyme catalyzed. This L-valyl ester prodrug of acyclovir is now undergoing clinical evaluation. The chemical syntheses and oral bioavailabilities of this group of esters will be presented.