116

Topical Bioavailability in Rats of the Antiviral Drug 2-Acetylpyridine Thiosemicarbazone. J.C. Drach, C.R. Eck, K. Perrott, J.P. Moreau, and C. Shipman, Jr. School of Dentistry, The University of Michigan, Ann Arbor, MI 48109, and Biomeasure, Inc., Hopkinton, MA 01748, U.S.A.

2-Acetylpyridine thiosemicarbazone (2-AcPyTSC) is an inhibitor of mammalian and herpes simplex virus (HSV) ribonucleoside diphosphate reductase. *In vitro* it inhibits the replication of HSV-1 in the low micromolar range. In the cutaneous herpes guinea pig model, it is highly efficacious at a concentration of 0.7% in 1,3-butanediol. A topical bioavailability study was performed by comparing the rate and extent of urinary and fecal excretion of radioactivity following topical and intravenous administration of [^{14}C]-2-ACPyTSC to male rats. For topical application, the drug was dissolved at 0.7% in 50 µl of 1,3-butanediol and applied at 1.1 mg/kg. In the IV study, the drug was administered in phosphate buffer at 0.7 mg/kg. After the last collection, animals were killed and the area around the injection site, the coat, and the whole carcass were assayed for radioactive content. Expired air contained only minor amounts of radioactivity and therefore was not a significant excretion pathway. The rates and extent of both urinary and fecal excretion were similar for both IV and topical administration (41 vs. 47% urine, 49 vs. 39% fecal; IV vs. topical, respectively). Biological half-lives estimated over the terminal urinary and fecal elimination phase were calculated to be 30 and 56 hours, respectively for IV injection and 43 to 50 hours, respectively for topical administration. Five days after topical administration approximately 7% of the dose was retained in the carcass. Excretion and retention data conformed to a pharmacokinetic three compartment model and suggest that certain tissue sites retain small amounts of the drug for extended periods. We conclude that 2-AcPyTSC in 1,3-butanediol has excellent topical bioavailability and that this is related to its topical anti-herpes activity. Sponsored by N.I.D.R. through grant RO1-DE08510.

117

SQ 32,756 (BV-araU): Characteristics and Pharmacokinetic Evaluation in Healthy Male Volunteers. J.W. Sherman, L.M. Kassalow, J.G. Harkins, B.J. Swites, B. Stouffer, D. Whigan, A.A. Sugerman, and S.A. Smith. The Squibb Institute for Medical Research and The Medical Center at Princeton, Princeton, N.J., USA.

SQ 32,756 (BV-araU) is a deoxythymidine analogue with marked in vitro activity against varicella-zoster virus (VZV) replication (ID_{50}=0.0013 mcg/mL). BV-araU requires the presence of viral-encoded thymidine and thymidylate kinases for conversion to the active triphosphate form which inhibits viral replication. When administered to 40 healthy male volunteers at doses ranging from 10-to 160-mg once daily for 14 days (n=8/group), the pharmacokinetic data (RIA and HPLC results) indicate that the mean values for AUC, Cmax, and Css of BV-araU were related to the dose of BV-araU. Values for Tmax, elimination $t_{1/2}$, and serum protein-binding of BV-araU were independent of dose. Tmax for BV-araU was approximately 3.3 hours. The serum elimination half-life for BV-araU was approximately 5 hours. Approximately 46% of the first administered dose of BV-araU was excreted in the urine over a 24-hour period as BV-araU. At steady-state, approximately 74% of the administered dose was excreted in the urine as BV-araU. After the administration of a single 10-mg dose, the mean peak serum concentration of BV-araU was 0.44 mcg/mL, whereas the mean trough serum concentration of BV-araU 24 hours after the dose was 0.04 mcg/mL with a range of 0.016 to 0.064 mcg/mL. The data suggest that BV-araU at a dose of 10-mg once daily may be suitable for the treatment of VZV infection since trough levels of drug at this dose far exceed the ID_{50} of the organism.