219

Efficacy and Pharmacokinetics of Topical HPMPC in a Guinea Pig Model of Genital Herpes. E.R. Kern[1], J. Palmer[1], P.E. Vogt[1], K. Cundy[2], M.J.M. Hitchcock[2], and J.-P. Sommadossi[1]. [1]University of Alabama School of Medicine, Birmingham, AL; and [2]Gilead Sciences, Inc., Foster City, CA, U.S.A.

Guinea pigs inoculated with herpes simplex virus (HSV) provide an ideal model for genital herpes in humans. In these animals HSV replicates to high titers in the vaginal tract and typical lesions form on the external genital skin. Topical treatment with 1%-3% (S)-1-[3-hydroxy-2-(phosphonyl-methoxy) propyl]cytosine (HPMPC) was highly effective in reducing viral replication and lesion severity. After parenteral administration of HPMPC, dose limiting nephrotoxicity has been observed in both animals and humans and there is concern that topically applied drug might be absorbed systemically with concomitant toxicity. Since topical HPMPC is currently in clinical studies for treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients, we used the guinea pig model for determining the absorption and excretion of topically applied radiolabeled HPMPC. After i.v. administration of 400 μg of ^{14}C-HPMPC, the plasma elimination half-life was about 12h. At 48h, 83% of the radioactivity was recovered in urine, 5% in kidney and 1% in feces. In contrast, after topical application of 100 mg of ^{14}C-HPMPC to genital skin, no drug was detected in plasma. At 48h, 4% of the radioactivity was recovered in urine, 0.1% in kidneys, and 10% in feces. These results indicate that topical HPMPC is very effective in this model infection and can be delivered without appreciable systemic absorption.

220

Inhibition of Dihydropyrimidine Dehydorogenase by 5-(*E*-2-Bromo-vinyl)uracil (BV-Ura) and Recovery of Rat Liver DPD Activity after Administration of BV-Ura or Sorivudine

H. Machida, K. Endo, Y. Watanabe, N. Ashida, and S. Sakata

R and D Division, Yamasa Corp., Choshi, Japan

Sorivudine (BV-araU), which shows the most potent anti-VZV activity *in vitro*, is effective in the treatment of herpes zoster and was approved as a new oral antiviral drug for the treatment of zoster in Japan 1993. However, the severe side effects occur when BV-araU is co-administered with 5-FU related anticancer drugs, and marketing of BV-araU had to be suspended. Dihydropyrimidine dehydorogenase (DPD), obtained from rat liver, was strongly inhibited by the pre-treatment with 5-(*E*-2-bromo-vinyl)uracil (BV-Ura) and other 5-substituted uracil analogues, but not by BV-araU and related nucleosides. Suppression of rat liver DPD activity was caused by administration of BV-araU (ca.50%) or BV-Ura (ca.80%). This suppression was accompanied with inhibition of plasma clearance of 5-FU. The DPD activity recovered to control level at 3 days after the last dose of 7 consecutive days doses of BV-araU or BV-Ura in the rats. Plasma clearance of 5-FU occurred as control 3 days and 5 days after cession of BV-araU and BV-Ura, respectively. In conclusion, the mechanism underlying the concomitant administration toxicity of BV-araU and 5-FU containing drugs is due to increased toxicity of 5-FU, which is caused by inhibition of DPD, the rate-limiting enzyme in pyrimidine catabolism, by BV-Ura, the metabolite of BV-araU, resulting in increases in blood concentration of 5-FU.