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Assessment of a Selective Inhibitor of HSV Thymidine Kinase (TK) as Therapy for Experimental Recurrent Genital Herpes. N.BOURNE*, F.J.BRAVO*, R.L.TOLMAN**, J.D.KARKAS**, L.R.STANBERRY* Children's Hospital Research Foundation, Cincinnati, OH. and ** Merck Sharp and Dohme Research Laboratories, Rahway, NJ.

HSV-coded TK is important in efficient reactivation of latent infection. These studies were designed to investigate whether treatment of latently infected animals with a TK inhibitor altered the natural history of recurrent HSV disease. 9-(((Z)-2-(hydroxmethyl)-cyclohexyl) methyl)guanine (L-653180) is a potent and selective non substrate inhibitor of HSV TK which can suppress or delay reactivation of HSV-1 from latently infected cells in vitro without affecting viral replication. In an initial study 6 female Hartley guinea pigs were treated with L-653180 in their diet (25mg/30g food) and water (300mg/L) for 7d. Blood, urine, kidney, liver, spinal cord and cerebral cortex specimens were collected. L-653180 was detected in all specimens at concentrations which, although low, were higher than the in vitro IC_{50} for the drug against HSV TK. In the second study 20 female Hartley guinea pigs were randomized into 2 groups following recovery from primary genital HSV-2 infection. One group received L-653180 in diet and water for 4 wk beginning 21d post-inoculation. Animals were examined daily for recurrent lesions for 10 wks. Although treated animals experienced fewer recurrences during treatment the results were not significantly different from controls, however, during the first 2 wk post treatment L653180-treated animals had significantly fewer recurrences than control animals ($p=.02$). Over the entire 10 wk, the difference was marginal ($p=.06$). These results suggest that inhibitors of viral TK may be useful in limiting reactivation of latent virus and thus recurrent infections. In these experiments the amount of drug that could be administered to the animals was limited by its poor solubility. Further studies with more potent and soluble inhibitors of HSV TK appears warranted

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Effect of Indomethacin on Recurrent Genital HSV-2 Infection in the Guinea Pig. N. Bourne[1], C.J. Harrison[2], D.F. Bratcher[1], D.I. Bernstein[3]. Children's Hosp Res Fdn[1], Cincinnati, OH, Creighton University[2], Omaha, NE and the Gamble Inst. Med. Res.[3] Cincinnati, OH.

We have previously demonstrated that systemic administration of the prostaglandin inhibitor indomlethacin (IND) reduced the incidence of UV-induced recurrent HSV-2 disease in the guinea pig. In this study we investigated its effect on spontaneous recurrent disease. Following recovery from primary genital HSV-2 disease 24 female Hartley guinea pigs were randomized to receive either IND at 10mg/kg I.M. or an equivalent volume of saline daily for 14 days (D21-34 P.I.). After a two week wash out period the groups were crossed over and treatment repeated (D49-62 P.I.). All animals were examined daily for recurrent lesions (D21-77 P.I.). During the first week of therapy the IND group had 50% fewer recurrent lesion days compared to controls (mean 0.9 vs. 1.8). This difference however was not observed during the second week. Following the washout, when recurrences were again equivalent between the groups, the 1group crossed over to receive IND developed fewer recurrent lesion days in both the first week (mean 0.5 vs. 1.1) and second week (mean 0.2 vs. 1.0) of therapy compared to the group now receiving placebo. When the data were combined IND treated animals developed significantly fewer recurrent lesion days during the two week period they received drug, compared to controls (mean 1.3 vs. 2.3, $p<.05$). IND appears to reduce recurrent genital HSV-2 disease perhaps by inhibiting prostaglandin induced local immune suppression.