197

Effect of HBPG on the Clinical Recurrences of Ocular Herpetic Keratitis in Squirrel Monkeys. HE Kaufman, ED Varnell, GE Wright*, and H Xu*, LSU Eye Center, New Orleans, LA and *University of Massachusetts Medical School, Worcester, MA USA.

HBPG [9-(4-hydroxybutyl)-N^2-phenylguanine] is a new viral thymidine kinase inhibitor that we tested for its ability to prevent recurrences of herpetic keratitis. Squirrel monkeys were infected in both corneas with Rodanus strain HSV-1. All corneas showed typical dendritic keratitis 3 days after infection, followed by spontaneous healing. Starting 14 days after infection, eyes were examined daily for clinical recurrences of herpetic keratitis. On day 21, the monkeys were randomized into two coded groups. One group received intraperitoneal (IP) injections of corn oil every 8 hours and the other group received IP injections of HBPG, 150 mg/kg, in a corn oil suspension every 8 hours. On day 22, room temperature was lowered in the late afternoon so that a low of 18°C was achieved during the night. After the morning treatment and examination on day 23, room temperature was raised to normal (24-27°C), and treatment was discontinued for that day and the following 3 days (days 24, 25, and 26). Treatment was reinstituted on day 27, the room temperature was lowered again on day 28, and treatment was again discontinued as before. A third cycle of treatment and cold stress was begun on day 34. Daily ocular examinations were continued until day 39, at which point the code was broken. We have previously shown that cold stress significantly increases the recurrences of herpetic keratitis in the squirrel monkey, and chose this model to test a promising thymidine kinase inhibitor using less drug than would be needed to study spontaneous recurrences with animals treated for 30 days. EY02672 (HEK); GM21747 (GEW).

198

Efficacy of Peptide T in the Rabbit Model of HSV-1-Induced Keratitis. EC Dunkel[1], J Michaelis[2], M Sleigh[2], J Guo[1], P Geary [1], and Q Zhu[1]. [1] Schepens Eye Research Institute; Department of Ophthalmology, Harvard Medical School, Boston, MA, USA and [2] Peptide Technology Limited, Dee Why, N.S.W., Australia.

Peptide T is an octapeptide initially developed as an anti-HIV agent. Peptide T has been reported to inhibit some actions of tumor necrosis factor and to reduce the incidence and/or severity of herpes related lesions. In this study, Peptide T topical therapy was evaluated during epithelial herpetic keratitis in the rabbit ocular model. NZW rabbits were inoculated with 10^3 pfu McKrae strain HSV-1 by topical drop instillation. On day 3 PI, all rabbits were evaluated by slit lamp biomicroscopy and ocular disease was graded on an increasing scale of severity. Animals were divided into groups with matched ocular disease, and topical therapy, 9x/day for 5 days was initiated as follows: Peptide T (10μg, 1μg, 100ng, 10ng, 1ng, 100pg, 10pg and 1 pg/ml), TFT, or Placebo Peptide 10 μg and 100ng/ml. TFT, was highly effective in reducing the development of HSV-1 ocular disease. Placebo Peptide therapy was not effective in slowing progression of HSV-1-induced disease. Topical Peptide T therapy demonstrated a biphasic response with enhanced anti-herpetic activity most evident in the physiological range (e.g. at 100 and 10ng/ml concentrations). At the higher Peptide T concentrations (μg/ml) the efficacy was blunted and the compound may have demonstrated a slight toxicity to the epithelial surface (epithelial cell sloughing). At the 10 and 1 pg/ml concentrations, Peptide T was ineffective in slowing HSV ocular disease progression. Clinical disease in the 100 and 10ng/ml Peptide T therapy groups was identical to TFT therapy. HSV recovery was reduced in the Peptide T and in TFT-treated eyes. Placebo peptide did not alter virus recovery. In the current study, Peptide T activity was 1,000 to 10,000 times more active than TFT (0.1% formulation). The development of a class of antiviral agents that are active in the ng/ml range will alleviate potential toxicity and drug resistance, problems currently encountered with nucleoside analog antiviral therapies.