II-24

Effect of Combination Therapy With Adenine Arabinoside (ara-A) and Acyclovir (ACV) in a Murine Model of Herpes Simplex Virus Type 1 (HSV-1) Encephalitis. E.R. Kern, P.E. Vogt, and J.C. Overall, Jr. Univ. of Utah Sch. of Med., Salt Lake City, Utah, USA.

Although treatment of HSV-1 encephalitis in humans with ara-A or ACV has reduced mortality and morbidity, the results of therapy have been less than optimal. The purpose of our studies was to determine if treatment with combinations of ara-A plus ACV is more effective than ara-A or ACV alone in a model of HSV-1 encephalitis. Groups of 15, 3 week old mice were inoculated intranasally with 10^6 pfu of HSV-1 and treated i.p. twice daily for 7 days beginning 24 h or 72 h after infection. Treatment regimens consisted of: 1) five concentrations of ara-A alone; 2) five concentrations of ACV alone; and 3) five combinations of ara-A plus ACV each having a ratio of 1 ED 50 of ara-A to 1 ED 50 of ACV. Final mortality rates were determined and drug ED 50 values for each treatment regimen were calculated using a Dose Effect Analysis computer software program. When therapy was begun at +24 h the ED 50 was 26.0 for ara-A alone and 4.8 for ACV alone. For combination treatment the ED 50 was reduced to 6.1 for ara-A and to 0.12 for ACV. For treatment begun at +72 h the ED 50 was 82.0 for ara-A alone and 16.0 for ACV alone. The ED 50 for the combination group was reduced to 25 for ara-A and 2.5 for ACV. Combination index values of 0.2 and 0.5 respectively indicated a strong synergistic interaction between ara-A and ACV in both experiments. These data indicate that a combination of ara-A plus ACV is synergistic in a murine model of HSV-1 encephalitis and suggest that this combination may be of benefit in the treatment of the human disease.

II-25

Comparison of Treatment with Adenine Arabinoside, 2', 3'-diacetate (ara-ADA) with Adenine Arabinoside (ara-A) and Acyclovir (ACV) in Herpes Simplex Virus (HSV) Type 1 Infections in Mice. P.E. Vogt and E.R. Kern, Univ. of Utah Sch. of Med., Salt Lake City, Utah, USA.

The purpose of this study was to compare the efficacy of a more soluble prodrug, ara-ADA, to ara-A and ACV in a murine model of HSV-1 encephalitis. Groups of 3 week old Swiss Webster mice were inoculated intranasally with 10^6 pfu of HSV-1 and treated i.p. twice daily for 7 days beginning 24, 48 or 72 h post-viral inoculation. Therapy with 200 mg/kg of ara-ADA significantly altered mortality when initiated as late as 48 h post infection. Protection was also observed with 100 or 50 mg/kg of ara-ADA given 24 h post-inoculation. Similar results were obtained with ara-A. In contrast, ACV significantly reduced final mortality when 60 mg/kg was initiated as late as 72 h after infection. With 30 or 15 mg/kg of ACV, protection was observed when treatment was begun at +48 h. We next determined the effect of these antiviral agents on the pathogenesis of an HSV-1 intranasal infection in mice. Treatment with 250 mg/kg of ara-ADA or ara-A, and 30 mg/kg of ACV was initiated 24 h post-viral challenge. On days 1-7, 10, 13, and 19 of infection, target organs were removed and assayed for presence of HSV-1. Viral replication in target organs were significantly reduced by all three antiviral drugs when compared to the placebo. However, under the conditions of this experiment, no significant differences between the three drugs were observed. These data suggest that ara-ADA is no more effective than ara-A and was less effective than ACV in the treatment of HSV-1 encephalitis in mice.