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N-Phosphonoacetyl-L-aspartate (PALA): an effective and safe broad spectrum antiviral. H.A. Blough (U.S. Bioscience, West Conshohocken, PA & *U.S. Army Medical Research Institute of Infectious Diseases, Frederick, MD 21702). K. Soike (Tulane U. Primate Center, Covington, LA 70433) W. Shannon (Southern Research Institute, Birmingham, AL 35255) P. Wyde (Baylor U., Houston TX 77030) & E. Dunkel, D. Pavan-Langston (Eye Res. Inst. & Harvard U., Boston, MA 02192).

At the onset of Operation "Desert Shield," one of us (HAB) was assigned the task of developing new molecular antivirals to counter endogenous threats in the Persian gulf area. As one of three potential approaches, PALA showed potent antiviral activity against many flavi- & bunyaviruses with $TI_{50}$ of > 30 at 10μg per ml (MTT); Additional assays revealed little or no toxicity against Vero, MK-2 and human foreskin fibroblasts. Further screening revealed good antiviral activity against cytomegalovirus (HCMV), varicella, respiratory syncytial virus (RSV), parainfluenza-3, vaccinia, influenza A & measles viruses (TI > 1300). When nucleotide pools were depleted, this antiviral effect was amplified. There was minimal effect against HIV-1 by RIPA of p18 (TI ca 5.0). No inhibitory effect was seen against HSV-1 or -2 and EBV. Plaque reduction assays confirmed the utility of this compound viz, when added 16 hrs post-infection, it caused a 2-3 $\log_{10}$ reduction in viral yields (HCMV, RSV & vaccinia) over 2-5 days at concs. of 3-20 μg/ml. The efficacy of PALA was further confirmed using in vivo models: at concs. of 10-50 mg/kg/day (as a single drug), lesions were markedly reduced and viral titer were decreased by 1-3 $\log_{10}$ in RSV (cotton rats), vaccinia (African green monkeys). PALA combined with DHPG, was better than the latter drug alone (additive) in treating HCMV retinitis (rabbit model); no toxicity was encountered over 3-14 days in various animal models. Molecular biological studies revealed inhibition of pyrimidine biosynthesis (aspartate transcarbamylase activity). These studies point to the development of a new series of broad spectrum antivirals, which are both potent and safe, for the treatment & prophylaxis of viral diseases in man.

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Antiviral Activity of (PALA) Alone and in Combination with Rifampicin Against Vaccinia Virus Induced Skin Lesions in African Green Monkeys. K. F. Soike[1], J.-L. Huang[1], P. Mack[1] and H. Blough[2], [1]Tulane Regional Primate Research Center, Covington, LA and [2]U.S. Bioscience, Inc., West Conshohocken, PA.

Phosphoacetyl-L-aspartate (PALA) is a broad spectrum antiviral which acts through inhibition of early steps in pyrmidine biosynthesis. We have evaluated PALA alone and in combination with rifampicin for ability to inhibit the development of skin lesions and virus replication following intradermal injections of vaccinia virus into 8 sites on the back of African green monkeys. Each injection site received 0.1 ml of virus containing $10^6$ $TCID_{50}$ of virus. Twice daily treatment with PALA at 50 mg/kg/day and/or rifampicin at 10 mg/kg/day was begun 24 hours after virus inoculation and continued for 10 days. An additional group of monkeys received PALA at 125 mg/kg given i.v. on days 1 and 7 p.i. Infection was monitored by daily scoring of skin lesion and titration of virus in 8 mm diameter skin biopsies taken on days 3, 7, and 10 p.i.

While rifampicin alone at 10 mg/kg/day was ineffective in reducing the severity of skin lesions and virus titers in the biopsied tissue PALA at 50 mg/kg/day alone or in combination with rifampicin, reduced both the severity of the lesions as well as the titer of virus in the skin. PALA at 125 mg/kg/day on days 1 and 7 p.i. was less effective in inhibiting lesion development and virus titer and was toxic resulting in the death of one of three monkeys. The results suggest that PALA, an inhibitor of asparate transcarbamylase and pyrimidine biosynthesis is capable of providing a therapeutic effect in clinical vaccinia virus infections.