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The Anti-VZV Agent 6-Methoxypurine Arabinoside: Neurotoxic Effects in 90-Day Oral Studies in Monkeys and Rats Given a Prodrug. G. M. Szczech and W. E. Tucker, Jr., Burroughs Wellcome Co., Research Triangle Park, NC 27709, U.S.A.

Signs of both central and peripheral neurotoxicity occurred in both monkeys and rats given the 2'-valerate ester of 6-methoxypurine arabinoside (170U88). It was given by gavage to monkeys (distilled water vehicle) and rats (0.5% methylcellulose vehicle) for 90 days. Groups of 5 male and 5 female monkeys (M. fascicularis) were dosed at 0, 25, 50, and 100 mg/kg/day. The daily dose was given in two installments with 6 hours between doses. Two of the 5 monkeys in each group were evaluated during an 8-week postdose recovery period. Two high-dose male monkeys and a mid-dose female monkey were necropsied for humane reasons before dosing was complete. They had signs of central nervous system toxicity including body tremors, incoordination, reduced activity, sleepiness, stupor, and lack of eye tracking first observed in the fifth week of dosing. Morphologic lesions diagnosed as axonopathy in sections of sciatic nerve occurred in monkeys at all dose levels but at the low dose in only 1 of 5 males and in 1 of 5 females. These were characterized by linear arrays of vacuoles along the course of occasional long axons. The axon filament was sometimes broken and occasionally there were accumulations of eosinophilic debris in the vacuoles. Neither the signs of central nervous system toxicity nor the axonopathy appeared to reverse in the postdose monkeys. Groups of 14 male and 14 female CD rats (Sprague-Dawley derived) were given single daily doses of 0, 150, 300, and 600 mg/kg. Ten/sex/group were necropsied at 90 days and 4 were necropsied at 4 weeks postdose. Morphologic and clinical signs of central nervous system toxicity in the rats consisted of groups of small vacuoles in cerebellar white matter at all dose levels and altered exploratory behavior at the high dose. Brain vacuoles were observed in rats examined at the end of the exposure period and in postdose recovery rats. Clinical signs of peripheral nervous system toxicity were limited to rats in the high-dose group. These consisted of hindquarter weakness, slow righting and placing reflexes, and ataxia. Again, these findings did not reverse in recovery rats. This toxicity profile was judged unacceptable for further development and clinical evaluation of 170U88.

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Comparison of Anti-Proliferative Activity of Selected Antiviral Agents in Human Cell Lines and a Bone Marrow Cell Assay.

C.B. Hartline, M.-Y. Xie, J.-P. Sommadossi, and E.R. Kern
Departments of Pediatrics and Pharmacology, University of Alabama School of Medicine, Birmingham, AL, USA

The initial evaluation of new antiviral compounds should include an assessment of toxicity in parallel with antiviral activity. A clonogenic assay using human bone marrow cells is considered the most predictive for drug induced marrow suppression in humans. However, this assay is not readily available and is too labor intensive for routine drug screening so a cell proliferation assay in an established cell line is often used. To identify a cell line that is both sensitive and relevant for detecting drug toxicity, we compared the growth inhibition of ten antiviral agents in four human cell lines with a human colony forming units - granulocyte, monocyte (CFU-GM) assay. Based on results of the CFU-GM assay, the drugs were segregated into three groups: 1) low toxicity (IC_{50} >10 μg/ml), ACV, ddI; 2) moderate toxicity (IC_{50} 1-10 μg/ml), DHPG, D4T, ddC, CBG; and 3) high toxicity (IC_{50} 0.1-1.0 μg/ml), HPMPC, FIAC, FIAU, AZT. Growth inhibition by these ten agents was determined in low passage human foreskin fibroblast (HFF) and three established cell lines, MRHF, HEL-299, and Hep-2 cells. For those agents that were toxic (Groups 2 and 3), the HFF and HEL-299 cells had IC_{50} values that were about 10-fold higher than those in the CFU-GM assay, whereas the MRHF and Hep-2 cells had IC_{50} values that were 25-100 fold greater than observed in bone marrow cells. The HFF and HEL-299 cells, therefore, were the most susceptible to growth inhibition by the antiviral agents tested and may be the most predictive for toxicity in the CFU-GM assay.