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Plasma and Cerebrospinal Fluid (CSF) Pharmacokinetics of Dideoxy-purine Nucleosides in Rhesus Monkeys, ME Hawkins, FM Balis,[†]K Murakami, [*]H Mitsuya, DG Poplack, National Institutes of Health, NCI, Pediatric Branch, [*] Clinical Oncology Program, Bethesda, MD, USA [†]Research Laboratory of Bioresources, Sanyo-Kokusaku Pulp Co., Yamaguchi, Japan.

The devastating affects of HIV encephalopathy underscore the importance of finding new anti-retroviral agents which penetrate into the CNS. The dideoxynucleosides (ddN) are effective in treating the systemic manifestations of AIDS. However, the CSF penetration of the ddN's ranges from > 20% for Zidovudine (AZT) to < 5% for dideoxycytidine (ddC) and the degree of penetration appears to correlate with the drugs' efficacy in AIDS dementia. The CSF penetration of the dideoxypurines, dideoxyinosine (ddI), dideoxyadenosine (ddA) and dideoxyguanosine (ddG) as well as two halogenated derivatives of ddG, 6'-Cl-ddG and 6'-I-ddG, were evaluated in a previously described nonhuman primate model. The halogenated ddG compounds are lipophilic prodrugs of ddG synthesized to improve the CNS penetration of ddG. Each drug was administered as a short intravenous infusion at doses of 1.5 g/M^2 (ddA, ddI) or 1.9 $mMol/M^2$ (ddG, Cl-ddG, I-ddG). Drug concentration (conc) in plasma and CSF was measured with a paired ion HPLC method. ddA was almost instantaneously deaminated to ddI and similarly Cl-and I-ddG were rapidly dehalogenated to ddG. The ratio of the area under the drug conc *vs* time curve (AUC) in CSF to that in plasma for ddI, after IV ddI or ddA, was 5%. The CSF to plasma ratio of ddG was 6.5% when ddG was given, 23% for Cl-ddG and 17% for I-ddG. However, the actual drug exposure to ddG (AUC) in the CSF did not differ significantly for the 3 analogues (12 μM•hr for ddG, 19 μM•hr for Cl-ddG, 9 μM•hr for I-ddG) following equimolar doses. The higher CSF:plasma ratios for the halo-ddG drugs were the result of lower plasma AUC's not higher CSF drug exposures. In summary the CSF penetration of ddI is lower than AZT and equivalent to ddC. Even though there appears to be an advantage for the halo-ddG drugs over ddG based on the CSF:plasma ratio, the actual exposure to ddG in CSF with equimolar doses appears to be similar.

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Open Study of Ribavirin Treatment in Patients with HIV Infection in Stage III and IV. Ruiz-Illescas R., Teran L., Garibay-Valencia M. Hospital Regional 20 de Noviembre, ISSSTE, Mexico City, Mexico.

Objectives: Evaluate if Ribavirin (Rb) (1) delays progression to AIDS; (2) reduce the incidence of opportunistic infections and the need for hospitalization during those episodes; and (3) prevent HIV-related immunocompromise.

Methods: Eighteen HIV-infected patients of both sexes, in stage III, IV-A and IV-C of disease according to CDC classification, were enrolled in an open study. Rb was administered at a daily dose of 800 mg. Response to treatment was monitored by CD4 and CD8 counts, CD4/CD8 ratio, and clinical evolution.

Results: Baseline and last mean values for CD4 and CD8 counts, and for CD4/CD8 ratios, shows no statiscally significant differences, and reduced incidence of opportunistic infections was observed. No clinical or laboratory side effects of has been observed during Rb treatment.

Conclusions: 1) Rb reduces incidence of opportunistic infections. 2) Rb prevents deterioration of the immune response in patients in stage III and IV of disease. 3) Rb delays disease progression in patients in stage III and IV of HIV infection.