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Use of SIV and HIV-2 infected monkeys in the evaluation of drugs against HIV/AIDS

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Screening for new drugs against HIV/AIDS in cell cultures infected with HIV has resulted in a large number of active inhibitors. Animal studies are necessary in order to select the best compounds for further development. An acute infection model in cynomolgus monkeys using SIV_{SM} and HIV-$2_{SBL6669}$ has been developed and used to determine the in vivo antiviral effects of AZT, PFA, ddC, ddI and FLT. The times for appearance of viral antigen and specific IgM were found to be useful parameters to record antiviral effects. Treatment starting 8 h prior to virus inoculation did not prevent infection when 10 - 100 monkey infectious doses were used but significant delays in appearance of antigen and specific IgM were recorded. Similar results were obtained for the SIV_{SM} and HIV-$2_{SBL6669}$ infections.

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Cellular Pharmacology of 2',3'-Didehydro-2',3'-dideoxythymidine (D4T) in Human Bone Marrow Progenitor Cells (HBMC). Zhu Z.*, H.T. Ho≠, M.J. Hitchcock≠, and J.P.Sommadossi*. *Department of Pharmacology, Center for AIDS Research, Univ. of Alabama at B'ham, B'ham, AL 35294, U.S.A.; ≠Pharmaceutical Research and Development Division, Bristol-Myers Squibb Co., Wallingford, CT 06492 U.S.A.

D4T is a potent anti-HIV agent with limited toxicity for HBMC (Mansuri et al. *J. Med. Chem.* 32:461-466, 1989). In the present study, the cellular pharmacology of D4T was investigated in HBMC in an attempt to clarify the observed low bone marrow toxicity. After exposure of HBMC to 10 μM [^{3}H]D4T, the D4T-5'-triphosphate (D4T-TP) was the predominant metabolite at 24 hr reaching a concentration of 0.3 pmol/10^6 cells and then slightly decreased from 24 to 48 hr. The D4T-5'-monophosphate levels were slightly lower, while the D4T-5'-diphosphate levels were about 6-fold lower than D4T-TP at 24 hr. Continuing elevation of D4T 5'-phosphate derivatives was observed during a 24-hr incubation period. Nucleic acids of HBMC exposed to 10 μM [^{3}H]D4T for 24 hr were purified and analyzed by cesium sulfate density gradient. No radioactivity was detected in the RNA region, whereas a significant amount was associated with the DNA region. The amount of D4T incorporated into DNA correlated with the initial extracellular D4T concentration. Hydrolysis of radiolabeled DNA and subsequent analysis by HPLC demonstrated incorporation of D4T and thymidine into DNA. Degradation of D4T to thymine and subsequent formation of thymidine was detected in HBMC. Pulse (24 hr)-chase (48 hr) experiments with 10 μM [^{3}H]D4T demonstrated that the concentration of radiolabeled D4T into DNA decreased over time during the chase. Under similar conditions, [^{3}H]3'-Azido-3'-deoxythymidine incorporated into DNA of HBMC did not decrease during the chase. Although D4T-TP standard and purified radiolabeled DNA were demonstrated to be slightly unstable after incubation at 37°C for 48 hr in phosphate-buffered saline (pH 7.4), this low unstability could not account for the amount of D4T excised from DNA. In conclusion, this study suggests that conversion of D4T to thymine and partial excision of D4T from DNA of HBMC result in a minimal incorporation of the drug into DNA consistant with the observed low cytotoxicity of this drug for HBMC.