

Intracellular Metabolism and Persistence of the Anti-Human Immunodeficiency Virus Activity of 2',3'-Didehydro-3'-Deoxy-4'-Ethynylthymidine, a Novel Thymidine Analog[∇]

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The therapeutic benefits of current antiretroviral therapy are limited by the evolution of drug-resistant virus and long-term toxicity. Novel antiretroviral compounds with activity against drug-resistant viruses are needed. 2',3'-Didehydro-3'-deoxy-4'-ethynylthymidine (4'-Ed4T), a novel thymidine analog, has potent anti-human immunodeficiency virus (HIV) activity, maintains considerable activity against multidrug-resistant HIV strains, and is less inhibitory to mitochondrial DNA synthesis in cell culture than its progenitor stavudine (D4T). We investigated the intracellular metabolism and anti-HIV activity of 4'-Ed4T. The profile of 4'-Ed4T metabolites was qualitatively similar to that for zidovudine (AZT), with the monophosphate metabolite as the major metabolite, in contrast to that for D4T, with relatively poor formation of total metabolites. The first phosphorylation step for 4'-Ed4T in cells was more efficient than that for D4T but less than that for AZT. The amount of 4'-Ed4T triphosphate (4'-Ed4TTP) was higher than that of AZTTP at 24 h in culture. There was a dose-dependent accumulation of 4'-Ed4T diphosphate and 4'-Ed4TTP on up-regulation of thymidylate kinase and 3-phosphoglycerate kinase expression in Tet-On RKO cells, respectively. The anti-HIV activity of 4'-Ed4T in cells persisted even after 48 h of drug removal from culture in comparison with AZT, D4T, and nevirapine (NVP). The order of increasing persistence of anti-HIV activity of these compounds after drug removal was 4'-Ed4T > D4T > AZT > NVP. In conclusion, with the persistence of 4'-Ed4TTP and persistent anti-HIV activity in cells, we anticipate less frequent dosing and fewer patient compliance issues than for D4T. 4'-Ed4T is a promising antiviral candidate for HIV type 1 chemotherapy.
