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NEW POTENTIAL ANTI-HIV PRODRUGS IN THE D4T SERIES

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To date azidothymidine is the only clinically approved drug among the 2',3'-dideoxynucleosides (ddN) analogues available for AIDS treatment. All these drugs must be phosphorylated intracellularly to their 5'-triphosphate derivatives to interact with the viral reverse transcriptase (RT). The rate and extent to which the ddN analogues are converted to their active (triphosphate) forms may be at least as important as their affinity for the target enzyme. Thus if D4T and AZT triphosphates appear to be equipotent in the RT inhibition, AZT is more readily converted to its monophosphate form but inhibits the thymidilate kinase needful for further phosphorylation. D4T is less efficiently converted to its monophosphate form but it does not inhibit thymidilate enzyme and further phosphorylation steps occur better than with AZT. To use this apparent biochemical advantage over AZT we have synthesized and evaluated some 5'-monophosphate D4T prodrugs and among them one cholesteryl or one palmityl derivatives fitted to increase the lipophilicity and improve the biotransport. The corresponding phosphate palmityl triester for which a cyanoethoxy group eliminates the last present charge was also prepared. Because a phosphate ester can liberate the nucleoside instead of the desired nucleoside monophosphate, bis 5'-D4T phosphate and its cyanoethoxy derivative were synthesized. As a control of the advantage of the phosphate moiety, the corresponding palmityl and cholesteryl D4T esters were prepared while the importance of the fatty chain was studied with the linoleic and linolenic esters. Cholesteryl D4T phosphate diester and bis 5'-D4T phosphate inhibited HIV replication in CEM-C113 cells more efficiently than D4T itself as measured by the reduction of the cytopathic effect based on MTT assay and reverse transcriptase activity. The two compounds were devoid of toxicity on CEM-C113 cells at doses equal to 50 and 100 μM respectively which brought selectivity index in the same range than AZT.

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Combination Chemotherapy: Antiviral Activity of AZT in Combination with Other Anti-HIV Agents, R.W. Buckheit, Jr., J. Germany-Decker, L. B. Allen, M. Hollingshead and W. M. Shannon. Southern Research Institute, Birmingham, AL, USA

Significant toxicity and the development of drug-resistant virus isolates are two hallmarks of patients undergoing AZT therapy to inhibit HIV infection. It is generally accepted that combinations of two or more drugs may be required to efficiently inhibit the spread of HIV in an infected individual and to prevent the pathogenic effects of the virus. We have been examining combinations of antiviral agents with AZT by the three dimensional analysis model of Pritchard and Shipman. Antiviral data for the drugs alone and in combination is obtained through a primary screening assay utilizing the XTT method for evaluating the ability of the compound to inhibit HIV-induced cell killing. Confirmation of these results may be obtained by analysis of reverse transcriptase activity in each sample. In addition we have performed combination studies utilizing murine leukemia virus to determine the relationship of our anti-HIV results with other model systems. We have performed numerous assays to determine the optimal conditions for the performance of these combination antiviral assays, including optimal multiplicity of infection and optimal cell type. We have also attempted to determine the type of drug, based on mechanism of action, that would give optimal benefit in combination with AZT. The drugs examined in combination with AZT have been chosen to represent different reported mechanisms of action. We will present the results of our combination antiviral analyses.