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Zidovudine-Uridine Dimer and its Hexadecyl Ester: Synthesis, Antiviral Evaluation and Pharmacokinetics. K.C. Agrawal, Q. Lu, M. Brakta, N. Bandera, S.R. Gogu and R.F. Garry. Depts. of Pharmacology and Microbiology & Immunology, Tulane University School of Medicine, New Orleans, LA 70112, USA.

Uridine was linked to zidovudine (AZT) via 5'-phosphate bond in an attempt to reduce AZT-induced hematopoietic toxicity. The dimer (AZT-P-U) was synthesized by condensing AZT-5'-β-cyanoethylphosphate with 2', 3'-O-isopropylideneuridine which upon hydrolysis produced the desired compound. Alternatively, the dimer was also synthesized by condensing 5'-hydrogenphosphonate of AZT with 2', 3'-di-O-acetyluridine in the presence of *bis*(2-oxo-3-oxazolidinyl) phosphoric chloride followed by oxidation with iodine. Tetrabutyl ammonium salt of the dimer was reacted with hexadecyl iodide to obtain the desired triester. The ED_{90} of AZT-P-U was 0.01μM versus 0.1μM for AZT against HIV-1 in MT4 cells. The AZT-P-U was 5-fold less toxic to erythroid progenitor cells with IC_{50} of 3.76μM versus 0.78 μM for AZT in the CFU-E assay using murine bone marrow cells. AZT-P-U (23.4mg/kg) upon i.p. administration in CD-1 mice was detected up to 4 hr. in serum, and was eliminated in a biphasic manner with an initial $t_{½}$ of approx. 8 min. The released AZT followed a similar pattern of pharmacokinetics as AZT itself. AZT-P-U was rapidly absorbed after oral administration and achieved peak plasma concentration within 15 min. Lack of 5'-OH group in AZT-P-U suggests that first pass metabolism of AZT in man may be avoided. The pharmacokinetics of the AZT-P-U will be compared with the triester synthesized to increase its brain permeability. The data indicate that AZT-P-U possesses potential advantages over AZT due to higher therapeutic index and superior pharmacokinetic properties. (Supported by NIAID grant AI-25909).

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Application of microdialysis to the study of antiviral drug pharmacokinetics in humans: validation of subcutaneous extracellular sampling of zidovudine

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Microdialysis is a method to sample the extracellular fluid. The method has previously been applied in animal studies of antiviral drugs and in clinical studies of antiepileptic drugs. By microdialysis it is possible to directly estimate the area under the time-conc curve (AUC) which is a measure of the exposure of the cells to the drug and this may be a more interesting measure in correlative studies with clinical effects and drug interactions and in studies of variability in bioavailability. We here report the application of microdialysis for the first time in man to sample an antiviral drug, zidovudine. Three healthy volunteers had a microdialysis probe implanted in abdominal subcutaneous adipose tissue. Day 1 the probe was left to adapt, day 2 the recovery of zidovudine was assessed by perfusing the probe with zidovudine at 0.5 and 1 µl/min and day 3 parallel blood sampling and microdialysis sampling was performed for 4 hours after oral intake of 200 mg zidovudine. The in vivo recovery of the probes was 75-92% at 0.5 µl/min which was used in the oral administration study. In all three volunteers there was a good correspondence between blood concentrations and microdialysis sample concentrations. It is concluded that microdialysis can be reliably used to sample extracellular zidovudine in man.