PHARMACOLOGICAL SIGNIFICANCE OF SELECTIVE UPTAKE OF NUCLEOSIDE ANALOGS BY VIRUS-INFECTED CELLS. N.K. Ayisi[1] and E De Clercq.[2] [1]Faculty of Veterinary Medicine, University of Maiduguri Nigeria, and [2]Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium.

Nucleoside analogs enter cells when they can affect some particular functions within the cells. This phenomenon is particularly true of anti-herpes simplex viral (anti-HSV) nucleosides. Virus induced functions trigger unknown mechanisms that cause cellular uptake of antiviral nucleosides independent of cell membrane alterations. Thus pharmacokinetic studies on antiviral nucleosides in healthy individuals may not reflect the correct situation in virus-infected individuals. High pressure liquid chromatographic (HPLC) analyses of serum and urine showed that bromovinyldeoxyuridine (BVdU) is metabolized in HSV encephalitis patients to BVdU-5'-monophosphate, BVdU-5'-diphosphate BVdU-5'-triphosphate, and bromovinyluracil (BVU). Others found only BVdU and BVU in serum of healthy individuals. The pharmacological significance of this phenomenon will be discussed with reference to absorption, distribution, metabolism, excretion, and structure-uptake/ structure-activity relationships.

Inhibition of human immunodeficiency virus (HIV) infection of fresh peripheral blood monocyte/macrophages (M/M) by dideoxynucleosides and phosphonoformate.
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We studied the ability of several dideoxynucleosides (ddN), 3'-azido-2'3'-dideoxythymidine (AZT), 2'3'-dideoxycytidine (ddC), 2'3'-dideoxyadenosine (ddA), and of phosphonoformate (PHOS) to inhibit HIV replication in fresh peripheral blood M/M. M/M were obtained by elutriation or by 2-hour adherence; they were always $\geq$90% esterase positive and OKM5$^+$, and <1% E-rosette positive. After exposure to a monocytotropic strain of HIV-1, Ba-L, in media alone or with the drugs, HIV-p24 production and reverse transcriptase (RT) activity were assessed every 7 days until day 42. >95% protection was consistently obtained with concentrations $\geq$20uM PHOS, $\geq$0.5uM AZT, $\geq$0.05uM ddC and $\geq$0.5uM ddA. The anabolic phosphorylation of ddC was studied in fresh M/M and in H9, a T4$^+$ cell line. After 24 hr cell exposure to 0.5uM tritiated ddC, the level of ddC-5'-triphosphate (ddCTP) was 0.91 and 0.82 pmole/10^6cells in fresh M/M and H9 respectively. Deoxycytidine kinase activity was comparable in fresh M/M and H9 cells (9.4 and 8.6 pmole dCMP/mg protein/ min respectively). The level of endogenous deoxycytidine triphosphate (dCTP), which competes with ddCTP at the level of RT, was 3.4 and 16.4 pmole/10^6cells respectively in fresh M/M and H9 cells. These results indicate that low concentration of ddN and PHOS inhibit HIV infection of fresh M/M (non-activated), and that at least for ddC, the low level of endogenous dCTP in M/M may contribute to the high level of antiviral activity.