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EFFECT OF INDOMETHACIN (INDO) ON ANTIVIRAL AND IMMUNE RESPONSE OF PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCs) FROM PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION.

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Background: metabolites of cyclooxygenase (CO) pathway of arachidonic acid play a key role in both antiviral and immunoregulatory function of IFN system. Aim: to evaluate the effect of CO pathway inhibition by INDO on 2,5-oligoadenylate synthetase (2,5OAS) and interleukin-2 (IL-2) synthesis by PBMCs of pts with HBV chronic hepatitis. Materials and Methods: 10^6 PBMCs/2ml of 16 HBV-positive pts were isolated and cultured for 24 hrs in absence or in presence of IFNα (1000 U/ml), INDO (5 μMol/l) or both. 2,5OAS (Eiken, Japan) and IL-2 (T Cell Diagn., USA) were directly assayed in the supernatants. Results analyzed by Student's t test for paired data are reported in the table.

	Unstimulated	IFNα	INDO	IFN+INDO
2,5OAS (pmol/ml)	$1.7 \pm 1.2^{a,b,c}$	2.6 ± 1.1^{a}	2.5 ± 1.3^{b}	2.8 ± 11^{c}
IL-2 (pg/ml)	$2.5 \pm 0.7^{d,e}$	$2.8 \pm 0.4^{d,f}$	2.7 ± 0.4^{g}	$3.0 \pm 0.4^{e,f,g}$

Data are expressed as M±SD of as $\log_{10}$; ^{a,b,d,e}: $p<.05$; ^{c,f,g}: $p<.01$

No significant correlations between HBV-DNA or ALT serum levels and both IL-2 and 2,5OAS were seen. Conclusions: CO inhibition seems able to enhance the antiviral and immune response induced by IFNα on PBMCs of HBV-positive pts. Based on this evidence, the inhibition of CO pathway might act as amplifiers of IFNα-induced antiviral and immune response, providing a support for the use of IFNα plus non steroidal antiinflammatory drugs combined therapy in HBV chronic infection.

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Lack of Pharmacokinetic Interaction Between Dipyridamole and Zalcitabine in Rats. C V Abobo and Y Xian, Pharmacy Practice, Texas Southern University, Houston, Texas 77004, U.S.A.

Although dideoxynucleoside monotherapy is no longer routinely recommended for treating HIV-1 infection, drug resistance had usually manifested following long-term monotherapy. This period appears to coincide with reduced dosage regimens which may contribute to decreased intracellular drug levels consequent on decreased peripheral blood circulation. In vitro studies have shown that cellular uptake of the dideoxynucleosides may be enhanced by dipyridamole (DPM). The purpose of this single dose study was to characterize the pharmacokinetics of zalcitabine (ddC) following concomitant administration with DPM. Rats were randomly assigned to either ddC or ddC plus DPM. ddC and DPM were dosed at 100 mg/kg and 15 mg/kg IV, respectively. Concentrations of ddC in plasma and urine were determined by HPLC. The Table below shows the pharmacokinetic parameters (mean ± SD) that were generated by area/moment analysis.

Parameters	ddC	ddC/DPM
AUC, mg*h/L	63.08 ± 13.65	72.04 ± 14.64
Cl, L/h/kg	1.66 ± 0.37	1.44 ± 0.30
Vdss, L/kg	1.17 ± 0.34	0.98 ± 0.38
$t_{\frac{1}{2}}$, h	1.03 ± 0.17	1.08 ± 0.22
fe, %	0.86 ± 0.11	0.77 ± 0.19

There were no statistically significant differences in the determined parameters, including the distribution coefficient (K_D) for ddC in both groups. Thus, the pharmacokinetics (including cellular uptake, as inferred from Vdss and K_D) of ddC were not significantly modulated by concomitantly administered dipyridamole.

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Pharmacokinetics of Dioxolane Guanine (DXG) Following Administration of DXG and Prodrug, (-)-β-D-2,6-Diaminopurine Dioxolane (DAPD), to Rats. H. Chen[1], F. D. Boudinot[1], A. Tang[1], Z. Gao[1], R. F. Schinazi[2], and C. K. Chu[1]. [1]College of Pharmacy, University of Georgia, Athens, GA 30602; and [2]Emory University School of Medicine, Emory University, Atlanta, Georgia 30322 and Georgia Research Center for AIDS and HIV Infections, Veterans Affairs Medical Center, Decatur, Georgia, 30033, USA.

DXG exhibits potent antiviral activity against HIV-1, HIV-2 and HBV in vitro. However, the limited aqueous solubility of DXG impedes its administration in vivo. DAPD, a prodrug of DXG, is more water soluble than DXG, thus, is more easily administered. DAPD is metabolized by adenosine deaminase yielding DXG. The purpose of this study was to characterize the pharmacokinetics of DXG following iv administration of 25 mg/kg DXG and DAPD to rats. Following administration of DXG, concentrations of the parent nucleoside declined biexponentially with a terminal phase half-life of 0.39 ± 0.02 h (mean ± SD). Total clearance of DXG was high relative to renal and hepatic blood flow rates, averaging 4.54 ± 1.05 L/h/kg. Renal clearance (2.68 ± 0.70 L/h/kg), which approached renal plasma flow indicative of active tubular secretion, accounted for approximately 60% of total clearance. Non-renal clearance of DXG was 1.86 ± 0.67 L/h/kg and steady-state volume of distribution of DXG was 2.14 ± 0.76 L/kg. Following administration of DAPD, prodrug concentrations declined with a terminal phase half-life of 0.88 ± 0.40 h^{-1}. DXG was rapidly generated from DAPD and approximately 90% of the DAPD dose was bioconverted to DXG. DXG concentrations subsequently decline in parallel with DAPD. Thus, DAPD administration extended the apparent half-life of DXG approximately 2-fold. The results of this study indicate that DAPD is efficiently converted to DXG in rats and provides for a sustained rate of formation of DXG. (NIH grants AI-25889 and AI-33655).

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Pharmacokinetic Studies of Dipalmitoyl-phosphatidyl-2',3'-Dideoxy-3'-thiacytidine (DPP-3TC) in Rodents.

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In an effort to improve the delivery of 2',3'-dideoxy-3'-thiacytidine (3TC) to lymphatic system, a phospholipid prodrug, dipalmitoylphosphatidyl-2',3'-dideoxy-3-thiacytidine (DPP-3TC), was synthesized. A high performance liquid chromatographic method was developed to determine concentrations of DDP-3TC and parent nucleoside in biological media. In vitro kinetic studies were performed in phosphate buffer and mouse serum, blood, liver homogenate, brain homogenate and muscle homogenate. DPP-3TC was stable in phosphate buffer, however, 3TC was released in all biological media. The highest rate of biotransformation of DDP-3TC to 3TC was observed in liver and brain homogenate. The in vivo disposition of the compounds were characterized following intravenous administration to mice and rats. DDP-3TC (25 mg/ml) was prepared by sonication of the compound in phosphate buffer at 44 °C. In mice, the half-life of 3TC in serum and lymph nodes was extended approximately seven-fold. Approximately 66% of the dose of DDP-3TC was converted to 3TC. The pharmacokinetics of DDP-3TC and 3TC were further assessed in rats. As seen in mice, prodrug administration resulted in an increased half-life of 3TC. After administration of 3TC, concentrations of the nucleoside fell below the limit of the assay after 4 h, however, 3TC concentrations were detectable for up to 8 to 12 h following administration of DDP-3TC. (NIH grants AI-25899 and AI-32351).