ELSEVIER

Antiviral Research 34 (1997) 91–99

Antiviral Research

Lymphatic targeting of anti-HIV nucleosides: distribution of 2′,3′-dideoxyinosine after intravenous and oral administration of dipalmitoylphosphatidyl prodrug in mice

Konstantine K. Manouilov [a], Zu-Sheng Xu [a], F. Douglas Boudinot [a], Raymond F. Schinazi [b], Chung K. Chu [a,*]

[a] *College of Pharmacy, University of Georgia, Athens, GA 30602, USA*
[b] *Georgia Research Center for AIDS and HIV Infections, Veterans Affairs Medical Center and Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Decatur, GA 30033-4004, USA*

Received 26 November 1996; accepted 27 November 1996

Abstract

In the search for prodrugs of 2′,3′-dideoxyinosine (ddI) with potential for improving the delivery of the nucleoside analogue to the lymphatic system, we synthesized dipalmitoylphosphatidyl-2′,3′-dideoxyinosine (DPP-ddI) and its pharmacokinetics were investigated in mice. The disposition of ddI in plasma and lymph nodes was examined following intravenous and oral administration of parent nucleoside (100 mg/kg) and DPP-ddI (400 mg/kg, equivalent to 100 mg/kg of ddI). Concentrations of ddI were determined by HPLC. Pharmacokinetic parameters were estimated by area/moment analysis. Intravenous administration of DPP-ddI resulted in a pattern of lower peak concentrations of ddI and more sustained exposure of parent nucleoside in plasma and lymph nodes compared to administration of the parent nucleoside. Both ddI and DPP-ddI yielded similar AUC values in lymph nodes. Oral administration of the prodrug resulted in lower concentrations and AUC values of ddI in plasma and lymph nodes when compared to administration of the parent nucleoside. The bioavailability of ddI following ddI and DPP-ddI administration was 15 and 8%, respectively. The results of the present study demonstrate that DPP-ddI administered intravenously shows potential for targeting and sustaining level of ddI in the nodular lymphatic tissues. © 1997 Elsevier Science B.V.

Keywords: Lymphatic targeting; 2′,3′-dideoxyinosine; Anti-HIV nucleosides

1. Introduction

During the initial clinically asymptomatic period of human immunodeficiency virus (HIV) in-

* Corresponding author. Tel.: +1 706 5425379; fax: +1 706 5425281; e-mail: dchu@rx.uga.edu

PII S0166-3542(96)01023-6

fection a profusion of viral replication occurs in the lymphatic system (Pantaleo et al., 1993, Embretson et al., 1993). Thus, lymphatic tissue is a major target for early antiviral drug therapy for HIV infection, and modes of enhancing the delivery of anti-HIV agents to this tissue are being sought. Currently, a number of phospholipid derivatives of antiviral compounds have been synthesized and tested for enhanced delivery to the lymphatic system and for biological activity (Hostetler et al., 1990, 1994; Manouilov et al., 1995; Xie et al., 1995). Among them are lipophilic phospholipid prodrugs dioleoylphosphatidyl-2′,3′-dideoxycytidine (DOP-ddC), dipalmitoylphosphatidyl-3′-azido-3′-deoxythymidine (DPP-AZT) and dipalmitoylphosphatidyl-3′-azido-2′,3′-dideoxyuridine (DPP-AZdU). Following administration of liposome formulations incorporating tritiated DOP-ddC and DPP-AZT, exposure to lymph nodes, as assessed by the area under the lymph node versus time curves of total radioactivity, were four- to five-fold greater when compared to after ddC or AZT administration itself (Hostetler et al., 1994). Administration of phospholipid prodrugs of AZT (DPP-AZT) and AZdU (DPP-AZdU) to mice produced improved lymph node exposure of the parent nucleosides, which resulted in higher concentrations of AZT and AZdU 2–3 h after prodrug administration. Further, half-life values for both nucleosides in serum and lymph nodes were three- to 15-fold greater following prodrug administration.

2′,3′-Dideoxyinosine (ddI) is a nucleoside analogue approved for the treatment of HIV infection. Clinical studies have suggested that ddI may be more effective than AZT in asymptomatic patients, as well as in patients with acquired immunodeficiency syndrome (AIDS) (Tartaglione et al., 1993; Murphy, 1995). Furthermore, ddI has several advantages over AZT, including activity against AZT-resistant strains of HIV, non-cell cycle phosphorylation dependence, longer intracellular half-life and minimal bone marrow suppression (Morse et al., 1993; Tartaglione et al., 1993). However, like AZT, some toxicity has been observed in individuals treated with ddI. Generally this toxicity is reversible on discontinuation of therapy.

With this information, it was of interest to explore the lymphatic distribution of ddI following administration of the parent nucleoside (ddI) and after administration of the prodrug, dipalmitoylphosphatidyl-ddI (DPP-ddI). The purpose of this study was to examine the pharmacokinetics and lymphatic system tissue distribution of ddI following intravenous and oral administration of ddI and DPP-ddI to mice.

2. Materials and methods

2.1. Chemicals

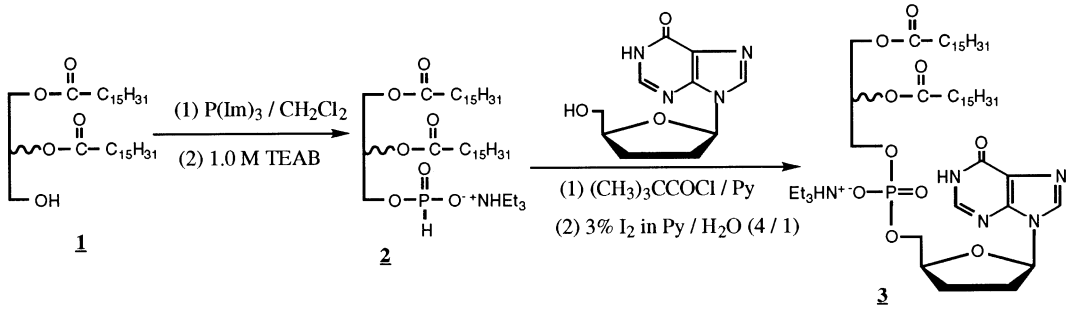
ddI was synthesized in our labs (Beach et al., 1992), DPP-ddI was synthesized as described below. 1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-methyluracil (L-FMAU), used as an internal standard for ddI quantitation, was synthesized as previously described (Chu et al., 1995). The chemical purity of the compounds, as assessed by spectral and HPLC analysis, was greater than 99%.

2.2. Synthesis of phospholipid conjugates of ddI (Scheme 1)

The NMR spectra were recorded on a Bruker AMX 400 spectrometer using TMS as internal standard for [^{1}H]NMR and 85% H_3PO_4 as external standard for [^{31}P]NMR, chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), and dd (doublet of doublet). TLC was performed on Uniplates (silica gel) purchased from Analtech. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. 1,2-Dipalmitoyl-rac-glycerol (**1**) was obtained from Sigma. Dry dichloromethane and pyridine were obtained by distillation from CaH_2 prior to use.

2.2.1. 1,2-Dipalmitoyl-rac-glycero-3-H-phosphonate, triethyl ammonium salt (**2**)

PCl_3 (1.42 ml, 16 mmol) was added to *N*-methyl morpholine (17.6 ml, 160 mmol) in 160 ml



Scheme 1. Synthesis of phospholipid conjugate of ddI.

dry CH_2Cl_2, and followed 1,2,4-triazole (3.68 g, 53.3 mmol). This mixture was stirred at room temperature for 30 min, then cooled to 0°C. A solution of **1** (1.82 g, 3.2 mmol) in anhydrous CH_2Cl_2 (40 ml) was added dropwise over 10 min. The reaction mixture was stirred for 15 min, then poured into 150 ml 1.0 M TEAB buffer (pH 7.2). The hydrous layer was extracted with CH_2Cl_2 (2×100 ml). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2:CH_3OH:NEt_3, 95:3:2) to afford product **2** (2.017 g, 86%): R_f, 0.52 (CH_2Cl_2:CH_3OH:NEt_3, 93:5:2); MS (ESI) 755.2 $(M + NEt_3 + Na)^+$; [^{31}P]NMR ($CDCl_3$) δ 5.24 ($J_{P\text{-}H} = 630$ Hz); [^{1}H]NMR ($CDCl_3$) δ 12.48 (br s, 1 H, D_2O exchangeable, $^+NHEt_3$), 6.74 (d, 1 H, $J_{P\text{-}H} = 630$ Hz, P-H), 5.15 (m, 1 H, CH-rac-2), 4.31 (dd, J = 3.4, 11.9 Hz, 1 H, CH_2-rac-3a), 4.11 (dd, J = 6.5, 11.9 Hz, 1 H, CH_2-rac-3b), 3.92 (m, 2 H, CH_2-rac-1), 2.99 (q, 6 H, CH_2 of NEt_3), 2.22 (m, 4 H, α-CH_2), 1.52 (br s, 4 H, β-CH_2), 1.15–1.28 (m, 57 H, 24 CH_2 and CH_3 of NEt_3), 0.81 (t, 6 H, CH_3).

2.2.2. 5′-(1,2-Dipalmitoyl-rac-glycero-3-phospho)-2′,3′-dideoxy inosine, triethyl ammonium salt (3)

A mixture of ddI (0.57 g, 2.42 mmol) and **2** (1.625 g, 2.2 mmol) was dried by co-evaporation with pyridine three times and dissolved in 25 ml of anhydrous pyridine. Pivaloyl chloride (0.82 ml, 6.6 mmol) was added under Argon and the mixture was stirred for 15 min. A solution of iodine (3% in pyridine:water = 4:1) was added to the reaction mixture until the appearance of a stable brown color of iodine was maintained. After 1.5 h, the excess iodine was reduced by the addition of saturated sodium thiosulfate solution. The mixture was evaporated, and the residue was partitioned between 1.0 M TEAB buffer (150 ml) and $CHCl_3$ (150 ml). The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$:CH_3OH:NEt_3, 93:5:2) to afford product **3** (0.96 g, 46.6%): R_f, 0.48 (CH_2Cl_2:CH_3OH:NEt_3, 44:5:1); MS, (FAB) 865 $(M\text{-}Et_3N\text{-}H)^+$; [^{31}P]NMR ($CDCl_3$) δ-0.17; [^{1}H]NMR ($CDCl_3$) δ 12.25 (br s, 1 H, D_2O exchangeable, NH^+Et_3), 11.79 (br s, 1 H, D_2O exchangeable, NH), 8.32 (s, 1 H, H-2), 7.90 (s, 1 H, H-8), 6.19 (br s, 1 H, H-1′), 5.18 (br s, 1 H, CH-rac-2), 3.98–4.31 (m, 7 H, H-4′, H-5′ and CH_2-rac-1,3), 3.04 (q, 6 H, CH_2 of NEt_3), 1.90–2.45 (m, 8 H, H-2′, H-3′ and α-CH_2), 1.50 (br s, 4 H, β-CH_2), 1.25 (br s, 57 H, 24 CH_2 and CH_3 of NEt_3), 0.82 (t, 6 H, CH_3); analytically calculated for $C_{51}H_{94}O_{10}N_5P \cdot 0.5\ CHCl_3$: C, 60.15; H, 9.26; N, 6.81. Found: C, 60.40; H, 9.43; N, 6.75.

2.3. Animals

Female NIH-Swiss mice (Harlan Sprague-Dawley, IN) weighing 24–26 g were used for pharmacokinetic experiments. Mice were maintained at the University of Georgia College of Pharmacy

Animal Care Facility, which is fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). The mice were acclimatized in a 12 h light/12 h dark constant-temperature (22°C) environment with free access to standard laboratory chow and water for 1 week prior to the experiments. Animal studies were approved by the University of Georgia Animal Care and Use Committee and conducted in accordance with guidelines established by the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.4. Pharmacokinetic studies

The disposition and lymph node distribution of ddI was examined following intravenous (iv) and oral (po) administration of 100 mg/kg ddI and after an equimolar dose (400 mg/kg) of DDP-ddI. For intravenous administration, ddI (25 mg/ml) was dissolved in physiological saline and injected into a tail vein over 1 min. For oral administration, ddI (12.5 mg/ml) dissolved in water, was administered by gastric gavage after instillation of 0.2 ml of Amphojel (Wyeth Laboratories, PA), used to prevent acid decomposition of ddI. A clear solution of DPP-ddI (33.3 mg/ml) was prepared by sonication of the compound in water at 26°C for 45 min using a Special Ultrasonic Cleaner (Laboratory Supplies Company, Hicksville, NY). HPLC analysis of DPP-ddI dosing solution demonstrated stability of the prodrug. Three hundred microliters (300 μl) of the solution was administered intravenously through a tail vein over 2–3 min or orally by gastric gavage. Animals were placed in individual cages and allowed food and water ad libitum. Mice (three animals per time point) were anesthetized with diethyl ether and sacrificed by exsanguination via a left ventricle heart puncture at 5, 15, 30 and 45 min, 1, 1.5, 2, 3, 4 and 6 h after drug administration. Blood (plasma) and neck (NLN), axillary (ALN) and mesenteric (MLN) lymph nodes were collected, and frozen until analysis. Plasma was immediately analyzed for nucleoside content.

2.5. Analytical methodology

Concentrations of ddI in plasma and lymph nodes were determined by high-performance liquid chromatography (HPLC). Plasma (200 μl) was mixed with 50 μl (10 μg/ml) of internal standard (L-FMAU) and 600 μl of acetonitrile while vigorously mixing to precipitate proteins. Tubes were centrifuged at $4000 \times g$ for 10 min and the supernatant was transferred into clean tubes and dried under a stream of nitrogen gas at 22°C. Lymph nodes were homogenized in 250 μl ice cold water and 50 μl of internal standard solution. Acetonitrile (1.8 ml) was added to precipitate proteins and tubes were centrifuged at $4000 \times g$ for 15 min at 4°C. Supernatant was transferred into clean tubes and dried under a stream of nitrogen gas at 22°C. The residue was reconstituted in 120 μl mobil phase and after centrifugation at $4000 \times g$ for 30 min, 25–50 μl was injected onto the HPLC.

Chromatographic separations were performed on a Shimadzu LC-10A series analytical HPLC system equipped with a Hypersil ODS column (Alltech Associates, 250×4.6 mm, 5 μm particle size) preceded by a guard column packed with μBondapak C18 precolumn insert (Waters, Milford, MA). The mobile phase consisted of 3% (v/v) acetonitrile, 30 mM K_2HPO_4 (pH 4.5) at a flow rate of 1.5 ml/min. The UV detection wavelength was 260 nm (0.001 AUFS). Under the chromatographic conditions described, ddI and internal standard retention times were 21 and 24 min, respectively. The limit of quantification for ddI was 0.1 μg/ml (or μg/g) in each biological media. The intra- and inter-assay relative standard deviations were less than 7% in plasma and tissue homogenates.

2.6. Data analysis

Mean plasma, NLN, ALN and MLN drug concentration versus time data were analyzed

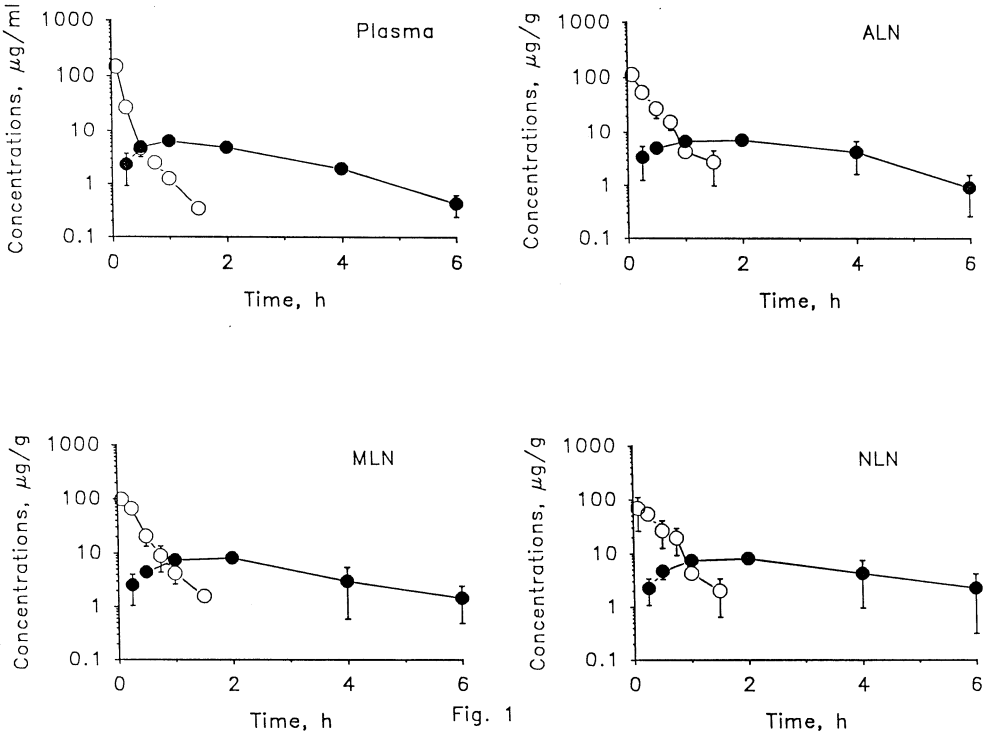


Fig. 1

Fig. 1. Mean (±S.D.) plasma, axillary (ALN), mesenteric (MLN) and neck (NLN) lymph node concentrations of ddI following intravenous administration of 100 mg/kg ddI (○) and an equimolar dose of DPP-ddI (●).

by non-compartmental techniques. The area under the plasma and lymph node concentration versus time curves (AUC) and the first non-normalized moments (AUMC) were determined by Lagrange polynomial interpolation and integration from time zero to the last sample time (Rocci and Jusko, 1983) with extrapolation to time infinity using the least-squares terminal slope (λ_z). Standard deviation of AUC values were calculated as previously described (Yuan, 1993). Half-life was calculated from $0.693/\lambda_z$. For intravenously administered ddI, total clearance (CL_T) was calculated from Dose/AUC and steady-state volume of distribution (V_{ss}) from Dose × AUMC/AUC^2. The bioavailabilty (F) of ddI following oral administration was calculated from AUC_{po}/AUC_{iv}. The relative exposure (r_e) of ddI in the lymph nodes was calculated from $AUC_{lymph\ node}/AUC_{serum}$.

3. Results

3.1. Intravenous administration of ddI and DPP-ddI

Concentrations of ddI in plasma and ALN, NLN and MLN as a function of time following bolus intravenous administration of 100 and 400 mg/kg DPP-ddI (equivalent to 100 mg/kg ddI) are illustrated in Fig. 1. Following iv administration of ddI, maximum observed concentrations of the nucleoside analogue in plasma and lymph nodes was observed at the earliest (5 min) sampling time. Subsequently, ddI displayed a rapid decline in plasma and lymph nodes concentrations with half-life values ranging from 0.25 to 0.33 h (Table 1). At all times, with exception of the 5 min sample, concentrations of ddI in lymph nodes were greater than or similar to those in plasma. No ddI was detected in serum or tissue samples collected after 1.5 h.

Table 1
Pharmacokinetics parameters of ddI following intravenous and oral administration of 100 mg/kg ddI and an equimolar dose of DPP-ddI to mice

	AUC mg/l per h		AUC_{LN}/AUC_{serum}		$t_{1/2}$ (h)	AUC_{po}/AUC_{iv}	
	IV	Oral	IV	Oral	IV	Oral	
ddI administration							
Plasma	42.5 ± 1.0	6.3 ± 0.3	1	1	0.26	0.30	0.15
Neck LN	34.4 ± 3.3[a]	11.2 ± 4.0	0.81	1.77	0.25	0.83	0.33
Axillary LN	39.4 ± 2.1	9.4 ± 10.4	0.92	1.49	0.33	0.67	0.24
Mesenteric LN	36.0 ± 1.9[a]	14.5 ± 14.1	0.85	2.29	0.27	0.74	0.40
DPP-ddI administration							
Plasma	19.7 ± 0.7	1.6 ± 0.2	1	1	1.28	1.07	0.08
Neck LN	38.1 ± 5.6[a]	4.2 ± 2.9	1.93	2.68	2.18	3.15	0.11
Axillary LN	29.6 ± 3.5[a]	5.1 ± 2.7	1.50	3.25	1.35	1.42	0.17
Mesenteric LN	31.2 ± 5.0[a]	4.0 ± 3.4	1.58	2.53	1.61	1.49	0.13

[a] Statistically significant difference ($P < 0.05$) between plasma and lymph nodes.

Pharmacokinetic parameters of ddI following intravenous administration of 100 mg/kg ddI to mice are presented in Table 1. The AUC value for ddI in ALN was similar to that in plasma. Statistically significant lower AUC values were observed in NLN and MLN. The relative exposure of the lymph nodes to ddI ranged from 0.81 to 0.92 in ALN. The total clearance and steady-state volume of distribution of ddI in mice were 2.35 l/h per kg and 0.88 l/kg, respectively.

Following intravenous administration of DPP-ddI, relatively low concentrations of ddI were detected in plasma and lymph nodes at 15 min (Fig. 1). Then levels of ddI increased and reached peak values between 1 and 2 h. Maximum concentrations of ddI were significantly lower than those after administration of ddI. Reaching peak value, ddI concentrations declined more slowly following DPP-ddI administration resulting in higher ddI concentrations after 45 min as compared to those after ddI itself administration, ddI was detected in plasma and lymph nodes for 6 h after administration of the prodrug. Concentrations of ddI after 5 min in the lymph nodes were significantly greater than those in plasma.

Pharmacokinetic parameters of ddI following intravenous administration of 400 mg/kg of DPP-ddI (equivalent to 100 mg/kg ddI) to mice are shown in Table 1. The AUC for ddI in plasma following iv administration of ddI was two-fold greater than that after intravenous prodrug administration. However, AUC values of ddI in lymph nodes were similar following administration of ddI or prodrug. The relative exposure of lymph nodes to ddI was greater than unity for each lymph node. The terminal phase half-lives of ddI in plasma and lymph nodes following iv administration of DPP-ddI were five- to nine-fold greater than those seen after administration of parent nucleoside.

3.2. Oral administration of ddI and DDP-ddI

Concentrations of ddI in plasma and axillary, neck and mesenteric lymph nodes following oral administration of 100 and 400 mg/kg DPP-ddI (equivalent to 100 mg/kg ddI) are illustrated in Fig. 2. Peak concentrations of ddI in plasma were observed 15 min following oral administration of the nucleoside analogue and maximum levels of ddI in lymph nodes were seen at 45 min ddI concentrations declined rapidly and no nucleoside was detected in serum or tissue samples collected after 1.5 h. Concentrations of ddI in the lymph nodes were similar to those observed in plasma, ddI concentrations following po administration of DPP-ddI were approximately ten-fold lower than those observed after po administration of ddI itself.

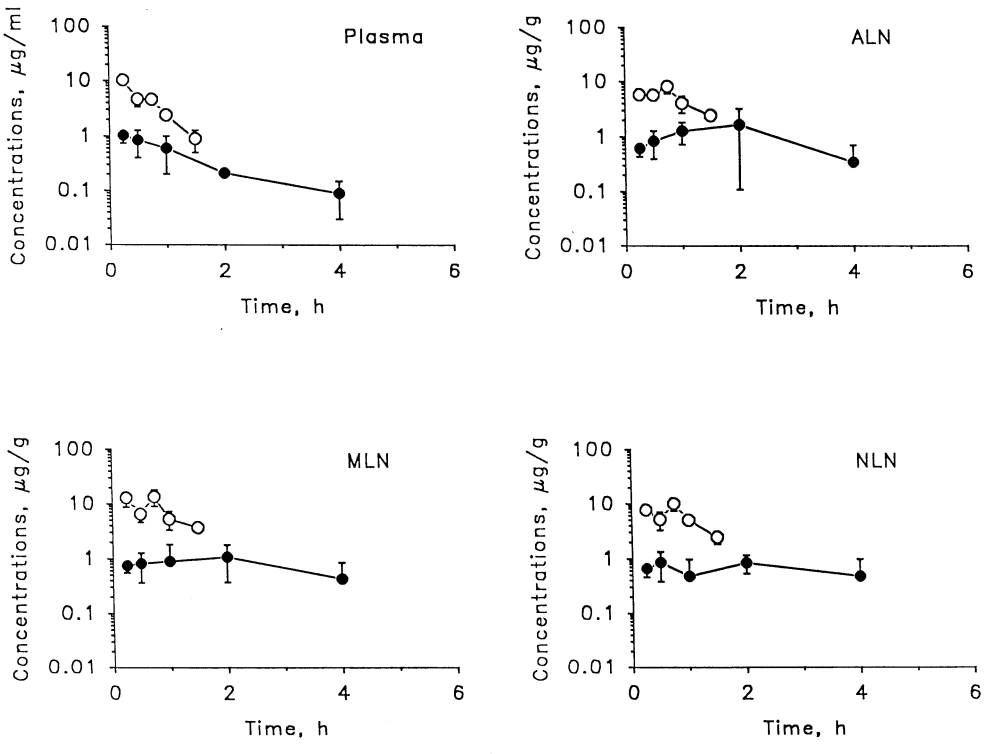


Fig. 2. Mean (± S.D.) plasma, axillary (ALN), mesenteric (MLN) and neck (NLN) lymph node concentrations of ddI following oral administration of 100 mg/kg ddI (○) and an equimolar dose of DPP-ddI (●).

Pharmacokinetic parameters of ddI following oral administration of 100 mg/kg ddI to mice are presented in Table 1. The oral bioavailability of ddI was 15%. The ratio of lymph node AUC values following po administration to those after iv administration were 0.32, 0.25, and 0.40 for NLN, ALN and MLN, respectively. The relative exposure of the lymph nodes to ddI after po administration of ddI was approximately two-fold greater than relative exposure following iv administration. Although the half-lives of ddI in plasma after po and iv administration of the nucleoside were similar, longer half-lives were seen in lymph nodes following po administration.

Low concentrations of ddI were observed following oral administration of DPP-ddI. Pharmacokinetic parameters of ddI following oral administration of 400 mg/kg of DPP-ddI (equivalent to 100 mg/kg ddI) to mice are shown in Table 1. The AUC for ddI in plasma following po administration of DPP-ddI was 4.5-fold lower than that after po administration of the parent compound. Further, the AUC for ddI in plasma after po administration of the prodrug was 12-fold lower than the AUC following intravenous administration of DPP-ddI. In terms of AUC values, accumulation of the nucleoside in lymph nodes was three times higher than in serum. The terminal phase half-lives of ddI in plasma and lymph nodes following po administration of DPP-ddI were similar to those seen after iv administration of the compound.

4. Discussion

The pharmacokinetic profiles of ddI in mouse plasma following intravenous and oral administration of ddI itself in the present study generally corresponded well with those that have been pre-

viously reported (Russell and Klunk, 1989). Both studies demonstrated a rapid decline in plasma ddI concentrations following intravenous and oral administration. However, the half-life of approximately 16 min reported here is greater than the value of 8.4 min reported by Russell and Klunk (1989) in mice administered 27.6 mg/kg ddI. The systemic clearance of ddI found here (2.35 l/h per kg) is lower than the value of 4.5 l/h per kg previously reported. These differences are likely due to better estimation of the half-life and AUC owing to increased assay sensitivity (0.1 compared to 0.4 μg/ml) of the HPLC method employed in the present study. Similar values for volume of distribution (0.9 l/kg) were found in both studies. The oral bioavailabilty of 15% found here is virtually identical to the bioavialability of ddI (13%) previously reported in mice (Russell and Klunk, 1989).

The ddI readily distributed into the lymphatic system. Following iv administration of ddI, concentrations of the nucleoside in lymph nodes were higher or similar to those observed in plasma. In contrast, the lymph node accumulation of AZT and AZdU were typically significantly less than that in serum. Further, the distribution of AZT and AZdU varied among lymph nodes whereas the distribution of ddI was similar in all three groups of studied lymph nodes.

Similar to results previously reported for phospholipid prodrugs of AZT, AZdU, and ddC (Hostetler et al., 1990, 1994; Manouilov et al., 1995), intravenous administration of DPP-ddI produced lower, but more sustained concentrations of ddI in plasma and lymph nodes when compared to the administration of parent nucleoside. The apparent half-life of ddI was extended four to five-fold following administration of DPP-ddI. While a lower AUC of ddI in plasma was observed after DPP-ddI, the AUC values in lymph nodes were similar to those obtained following intravenous administration of ddI. As a result, the ratio of the AUC of ddI in lymph nodes relative to the AUC in plasma (relative exposure) as compared to administration of parent nucleoside was greater following prodrug. In contrast, intravenous and oral administration of DPP-AZT and DPP-AZdU to mice has been shown to increase AUC values, as well as relative exposure of parent compound in lymph nodes when compared to administration of AZT and AZdU.

The oral bioavailability of DPP-ddI was low (8%). In vitro studies demonstrated that DPP-ddI was stable at pH 1, however, the prodrug precipitated from solution. Thus, the low oral bioavailability of ddI from DPP-ddI is likely due to precipitation of DPP-ddI in acid environment of the stomach and resulted in poor absorption of prodrug. DPP-ddI administered orally yielded more sustained levels of ddI in serum and lymph nodes compared to administration of nucleoside itself. However, the lymph node ddI AUC values following oral administration of DPP-ddI were lower than those after oral administration of parent nucleoside.

In summary, intravenous administration of DPP-ddI resulted in a pattern of lower peak concentrations of ddI and more sustained exposure of parent nucleoside in plasma and lymph nodes compared to administration of the parent nucleoside. Oral administration of the prodrug, resulted in lower concentrations and AUC values of ddI in plasma and lymph nodes when compared to administration of the parent nucleoside. However, relative exposure values were two-fold higher than after ddI administration itself. Thus, DPP-ddI administered intravenously shows potential as a prodrug for targeted delivery of ddI to the nodular lymphatic tissues. More studies are required to elucidate the favorable changes of relative exposure of ddI in lymph nodes following oral administration of phospholipid prodrug.

Acknowledgements

This work was supported in part by Public Health Service grants AI-25899 and AI-32351 from the National Institutes of Health and by the Department of Veterans Affairs.

References

Beach, J.W., Kim, H.O., Jeong, L.S., Nampalli, S., Islam, Q.,Ahn, S.K., Babu, J.R. and Chu, C.K. (1992) A highly stereoselective synthesis of anti-HIV 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides. J. Org. Chem. 57, 3887–3894.

Chu, C.K., Ma, T.W., Shanmuganathan, K., Wang, C.G., Xiang, Y.J., Pai, S.B., Yao, G.Q., Sommadossi, J.-P., and Cheng, Y.-C. (1995) 2′-Fluoro-5-methyl-β-L-arabinofuranosyl (L-FMAU) as a novel antiviral agent for hepatitis B and Epstein–Barr virus. Antimicrob. Agents Chemother. 39, 979–981.

Embretson, J.M., Zupancic, Ribas, J.L., Burke, A., Racz, P., Tenner-Racz, K., and Haase, A.T. (1993) Massive covert infection of helper T-lymphocytes and macrophages by HIV during the incubation period of AIDS. Nature 362, 359–364.

Hostetler, K., Stuhmiller, L.M., Lenting, H.B.M., van den Bosch, H. and Richman, D.D.(1990) Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides. J. Biol. Chem. 265, 6112–6117.

Hostetler, K.Y., Richman, D.D., Sridhar, C.N., Felgner, P.L., Felgner, J., Ricci, J., Gardner, M.F., Selleseth, D.W. and Ellis, M.N. (1994) Phosphatidyl-azidothymidine and phosphatidyl-ddC: assessment of uptake in mouse lymphoid tissues and antiviral activities in human immunodeficiency virus-infected cells and in Rauscher leukemia virus-infected mice. Antimicrob. Agents Chemother. 38, 2792–2797.

Manouilov, K.K., Fedorov, I.I., White, C.A., Boudinot, F.D., Kotra, L.P, Schinazi, R.F., Hong, C.I. and Chu, C.K. (1995) Targeting for the lymphatic system by an anti-HIV nucleoside prodrug dipalmitoylphosphatidyl-AZDU (DPP-AZDU) and dipalmitoylphosphatidyl-AZT (DPP-AZT). Antiviral Chem. Chemother. 6, 230–238.

Morse, G.D., Shelton, M.J. and O'Donnell, A.M. (1993) Comparative pharmacokinetics of antiviral nucleoside analogues. Clin. Pharmacol. 24, 101–123.

Murphy, R. (1995) Clinical aspects of human immunodeficiency virus disease: clinical rationale for treatment. J. Infect. Dis. 171 (Suppl. 2), S81–S87.

Pantaleo, G., Graziosi, C., Demarest, J.F., Butini, L., Montroni, M., Fox, C.H., Orenstein, K.M., Kotler, D.P. and Fauci, F.A. (1993) HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature 362, 355-358.

Rocci, M.L. and Jusko, W.J. (1983) LAGRAN program for area and moments in pharmacokinetic analysis. Comp. Prog. Biomed. 16, 203–216.

Russell, J.W. and Klunk, L.J. (1989) Comparative pharmacokinetics of new anti-HIV agents: 2′,3′-dideoxyadenosine and 2′,3′- dideoxyinosine. Biochem. Pharmacol. 38, 1385–1388.

Tartaglione, T.A., Fletcher, C.V. and Collier, A.C. (1993) Principles and management of acquired immunodeficiency syndrome. In: Pharmacotherapy. A pathophysiologic Approach (DiPiro, J.T., Talbert, R.L., Hayes, P.E., Yee, G.C., Matzke G.R. and Posey, L.M., eds), pp. 1837–1867, Appleton and Lange, Norwalk, CT.

Xie, H., Voronkov, M., Liotta, D.C., Korba, B.A., Schinazi, R.F., Richman, D.D. and Hostetler, K.Y. (1995) Phosphatidyl- 2′,3′-dideoxy-3′-thiacytidine: synthesis and antiviral activity in hepatitis B- and HIV-1-infected cells. Antiviral Res. 228, 113–120.

Yuan, J. (1993) Estimation of variance for AUC in animal studies. J. Pharm. Sci. 82, 761–763.