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Single-Dose Pharmacokinetics of Delavirdine Mesylate and Didanosine in Patients with Human Immunodeficiency Virus Infection

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Delavirdine is a nonnucleoside reverse transcriptase inhibitor with in vitro activity against human immunodeficiency virus type 1 (HIV-1) that is currently being evaluated in combination regimens with various nucleoside analogs, including didanosine. Due to the pH-dependent solubility of delavirdine, the buffering agents in didanosine formulations may reduce delavirdine absorption. To evaluate the potential interaction between these agents, 12 HIV-infected patients (mean [± standard deviation] $CD4^+$ cell count, 304 ± 213/mm^3) were enrolled in a three-way crossover single-dose study. Didanosine (125 to 200 mg given as buffered tablets) and delavirdine mesylate (400 mg) pharmacokinetics were evaluated when each drug was given alone (treatments A and B, respectively), when the two drugs were given concurrently (treatment C), and when didanosine was given 1 h after delavirdine (treatment D). Delavirdine exposure was reduced by concurrent administration of didanosine. The maximum drug concentration in serum (C_{max}) was reduced from 7.22 ± 4.0 to 3.51 ± 1.9 μM, and the area under the concentration-time curve from 0 h to infinity ($AUC_{0\rightarrow\infty}$) was reduced from 22.5 ± 14 to 14 ± 5.7 μM · h. The extent of N-dealkylation, as indicated by the ratio of the N-dealkylated delavirdine $AUC_{0\rightarrow\infty}$ to the delavirdine $AUC_{0\rightarrow\infty}$, was unchanged across study treatments ($P = 0.708$). Reductions in didanosine exposure were observed during concurrent administration with delavirdine with a C_{max} reduction from 4.65 ± 2.0 to 3.22 ± 0.59 μM and an $AUC_{0\rightarrow\infty}$ reduction from 7.93 ± 3.9 to 6.54 ± 2.3 μM · h. Thus, concurrent administration of delavirdine and didanosine may reduce the $AUC_{0\rightarrow\infty}$ of both drugs, although the clinical significance of this reduction is unknown. Administration of delavirdine 1 h before didanosine avoided the interaction. Due to the single-dose nature of this study, these findings require further evaluation at steady state.

Delavirdine is a bisheteroarylpiperazine nonnucleoside reverse transcriptase inhibitor (NNRTI) which has in vitro activity against human immunodeficiency virus type 1 (HIV-1) with a 50% inhibitory concentration of 0.26 μM (11, 12). Since HIV-1 has been noted to develop rapid *in vitro* and *in vivo* resistance to other NNRTIs (i.e., nevirapine, pyridinone, and atevirdine; [19, 26]), NNRTIs are being investigated primarily in combination regimens (9). The combination of delavirdine and didanosine with or without zidovudine has demonstrated synergy in vitro (4). However, didanosine is acid labile and necessitates a buffered formulation to prevent intragastric degradation (1), while delavirdine is most soluble at a pH of <2 (5a). Thus, concurrent administration of didanosine with delavirdine may potentially reduce the absorption of delavirdine. The present study was undertaken to evaluate the potential drug interaction between didanosine and delavirdine by comparing the pharmacokinetic parameters of the drugs when given alone, concurrently, and 1 h apart (delavirdine prior to didanosine).

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MATERIALS AND METHODS

This trial was an open-label pharmacokinetic study of single doses of didanosine and delavirdine given to 12 HIV-infected individuals between the ages of 18 and 55 years who were receiving chronic didanosine therapy. All study subjects had documented HIV infection and a $CD4^+$ cell count of <500/mm^3 within 30 days of study entry. For all subjects, a complete medical history, a physical examination with vital signs, and a resting 12-lead electrocardiogram were completed during the screening period. The following laboratory criteria were required for study entry: hemoglobin, >9.5 g/dl; absolute neutrophil count, >1,000/mm^3; platelet count, >100,000/mm^3; serum creatinine of <1.6 mg/dl or estimated creatinine clearance of >50 ml/min; hepatic enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) <2.5 times the upper limit of normal; bilirubin, <2.5 mg/dl; negative urine screen for drugs of abuse; and no active substance abuse. The subjects agreed to abstain from alcohol from 48 h prior to the beginning of the study and through the final blood drawing. Subjects were ineligible if one or more of the following conditions were present: clinically significant cardiovascular, renal, hepatic, cardiac, pulmonary, endocrine, hematologic, vascular, or collagen disease; any acute medical problems requiring hospitalization; neurologic or psychiatric disorders which could impair patient compliance; use of any investigational agents within 15 days prior to the study; receipt of any known hepatic enzyme-inducing or -inhibiting agents or anticholinergics for 30 days prior to the study period; use of antacids within 1 week prior to entry into or during the study; a history of hypersensitivity to piperazine-type drugs; and pregnancy or breast feeding. The protocol was approved by the Institutional Review Board, and informed consent was obtained prior to study entry.

The study was conducted on 4 separate days in a clinic setting with the subjects arriving on the morning of each study phase. The subjects fasted from midnight until 4 h after dosing on each of the 4 study days. All meals consumed during the study periods were isocaloric (regular diets), and the subjects were asked to consume the entire meal over a 30-min period. All morning doses were administered by clinic personnel. All subjects received their usual didanosine dose or its equivalent in a tablet formulation (treatment A) on day 1. Thereafter, subjects randomly received 400 mg of delavirdine mesylate in the following study treatments in a randomized order: treatment B was administration of delavirdine alone, treatment C was concurrent administration of delavirdine with didanosine, and treatment D was administration of delavirdine followed by di-

TABLE 1. Demographic characteristics of subjects

Subject no.	Age (yr)	Gender[a]	Race[b]	Wt (kg)	No. of CD4 cells/mm^3[c]	Smoking status[d]	Noninvestigational medication[e]
1	30	M	C	72.3	481	NS	Didanosine, 200 mg q 12 h
2	45	M	C	73.0	591	NS	Didanosine, 200 mg q 12 h
3	31	M	C	73.5	459	S	Didanosine, 200 mg q 12 h; amoxicillin-clavulante, 2,000 mg/day
4	38	M	A	72.6	20	NS	Didanosine, 200 mg q 12 h; TMP/SMZ DS daily, clotrimazole troches
5	40	M	C	85.7	351	S	Didanosine, 200 mg q 12 h; acyclovir, 2,400 mg/day; TMP/SMX DS; 3 times/wk
6	42	M	C	80.7	227	NS	Didanosine, 250 mg q 12 h; acyclovir, 800 mg/day
7	43	M	C	58.1	39	S	Didanosine, 200 mg q 12 h; TMP/SMX DS daily
8	38	M	C	98.9	516	S	Didanosine, 200 mg q 12 h; TMP/SMX DS daily
9	33	M	C	79.8	133	NS	Didanosine, 250 mg q 12 h; TMP/SMX DS, 5 times/wk; acyclovir, 600 mg/day
10	35	F	C	47.2	65	NS	Didanosine, 250 mg q 24 h; pentamidine inhalant, 300 mg q mo; albuterol 10 mg q 4 wks
11	43	F	A	65.8	457	S	Didanosine, 200 mg q 12 h
12	42	F	C	53.6	42	S	Didanosine, 125 mg in study
Mean ± SD	38 ± 5.2			73.4 ± 13.7	304 ± 213		

[a] M, male; F, female.
[b] C, Caucasian; A, African-American.
[c] CD4 cell count at screening (within 14 days of study entry).
[d] S, smoker; NS, nonsmoker.
[e] Medications taken during the 12-day study period. q; every; TMP/SMX, trimetheprim-sulfamethoxazole; DS, double strength.

danosine 1 h later. The latter three study treatments were separated by a minimum of 5 days. All subjects continued to receive their previously prescribed didanosine regimen, but not delavirdine, during the period between study treatments.

Pharmacokinetic assessments were done during each of the four study treatments. A 5-ml whole-blood sample was withdrawn from an indwelling intravenous cannula into a heparin-containing tube at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after administration of drug doses. Plasma was harvested by centrifuging the specimens at 1,000 to 2,000 × *g* for 10 min. The upper plasma layer was transferred to a storage vial and stored at −20°C. All samples were then transported on dry ice by overnight courier for drug assay.

Drug assays. (i) delavirdine. Delavirdine concentrations in plasma were determined by high-performance liquid chromatography by an assay procedure developed at Pharmacia & Upjohn, Inc. (15). Delavirdine and its N-dealkylated metabolite (N-DLV) were extracted from plasma by protein precipitation with an acetonitrile-containing internal standard mixture (U-88822; Pharmacia & Upjohn, Inc.). After centrifugation, the supernatant was diluted 1:2 with 10 mM potassium phosphate buffer and directly injected into the chromatographic system. The compounds were measured by fluorescence detection with excitation at 302 nm and emission filtration at 425 nm. Peak height ratios of delavirdine to the internal standard and N-DLV to the internal standard were calculated and used to formulate a calibration curve of concentration (x) versus peak height ratio (y) by using weighted (1/concentration^2) least-squares linear regression. Concentrations of delavirdine and N-delavirdine in plasma in quality control and patient samples were determined from the calibration curves. Delavirdine plasma standards of 0.181 to 86.8 μM (0.174 to 72.4 μM for N-DLV) were used to determine the calibration curves. The limit of quantitation was typically 0.11 μM. Interday coefficients of variation for the high, medium, and low quality controls were routinely <7% each. Intraday variability ranged from 1 to 10%.

(ii) Didanosine. Didanosine concentrations in plasma were measured by radioimmunoassay with reagents purchased from Sigma Chemical Co. (St. Louis, Mo.) (10). All reagents were equilibrated to room temperature before use. One hundred-microliter volumes of standard, control, and unknown plasma samples were pipetted into borosilicate glass tubes in duplicate. One hundred microliters of ^{3}H-labelled tracer and 100 μl of a working dilution of rabbit anti-didanosine serum were added to all tubes, except the tubes used to determine total counts and nonspecific binding. All tubes were vortexed briefly and incubated at room temperature for 2 h. Afterwards, 1 ml of the secondary (anti-rabbit) antibody was pipetted into each tube, except the tube used for total-count determination, and vortexed briefly. Excluding the total-count tubes, all tubes were placed into a precooled centrifuge chamber at 4°C and incubated for 30 min. After incubation, the tubes were centrifuged for 1 h at 2,200 × *g*. The supernatant was decanted, and the pellet was resuspended in 0.1 N HCl. The contents of each tube were transferred to scintillation vials containing 5 ml of scintillation fluid, the radioactivity of which was then counted for 5 min in a 1409 DSA-based liquid scintillation counter (Wallac, Gaithersburg, Md.). Total counts were 15,000 to 24,000 dpm, and nonspecific binding ranged from 62 to 246 dpm. A four-parameter equation was used to fit the standard curve by utilizing the RiaCalc. LM version 2.65 software package (Wallac). Variation was typically 3 to 10%, with larger variation seen at the highest standard concentration. The fit of the standard curve was not biased, as it exhibited a good scatter of positive and negative errors with respect to the concentration range. Intraassay variations ranged from 0.3 to 3% at 30 ng/ml (0.127 μM). Interassay variations were 7, 10, and 9% at 2, 5, and 30 ng/ml, respectively. The limit of quantitation for the assay was typically 0.008 μM.

Pharmacokinetic and statistical analyses. Plasma concentration data for delavirdine and didanosine were plotted on a log-linear graph of concentration versus time since dose administration. Pharmacokinetic analysis was performed by using noncompartmental methods in PCNONLIN (SCI Software, Lexington, Ky.). The area under the concentration-time curve from 0 h to infinity ($AUC_{0\to\infty}$) was adjusted for any measurable drug at the baseline (C_{0h}) by subtracting the estimated area under the baseline value (i.e., adjusted $AUC_{0\to\infty} = AUC_{0\to\infty} - C_{0h}/k_{el}$, where k_{el} is the elimination rate constant) For subjects receiving didanosine doses other than 200 mg, the maximum drug concentration in serum (C_{max}) and $AUC_{0\to\infty}$ were normalized to the values anticipated with 200-mg doses prior to determination of mean values and statistical analysis. (Didanosine has been shown to exhibit linear pharmacokinetics over a dosage range of 0.8 to 10.2 mg/kg [16].) Oral clearance was determined by dose/$AUC_{0\to\infty}$. Due to the sequential order of didanosine treatments (i.e., all subjects received treatment A first), nonparametric comparisons were thought to be appropriate. Pairwise comparisons of pharmacokinetic parameters were made between treatment groups by the Wilcoxon signed rank test (Systat; Systat, Inc., Evanston, Ill.). Since the order of delavirdine treatments was randomized, delavirdine pharmacokinetic parameters were first compared by using analysis of variance (ANOVA). Each pharmacokinetic parameter was treated as a continuous variable. The fixed effects evaluated for each parameter were: period, order, and treatment. When significant differences were identified across study treatments, pairwise comparisons were made with the Bonferroni test. The delavirdine pharmacokinetic parameters for each treatment also were compared via the Wilcoxon signed rank test.

RESULTS

Subjects. Twelve subjects were enrolled in the study and completed it without clinically significant medical events. The subject demographics are listed in Table 1. Two female subjects (no. 10 and 12) received 125 mg of didanosine (given as one 100-mg tablet and one 25-mg tablet) during the study due to low body weight. Two subjects were taking the powder for oral suspension formulation prior to the study but received the equivalent dose of the tablet formulation during the study. Concurrent study medications were not administered during pharmacokinetic study days.

TABLE 2. Delavirdine pharmacokinetic parameters determined for treatments B, C, and D

Treatment or statistical test	Mean value for delavirdine ± SD or *P* value						
	T_{max} (h)	C_{max} (μM)	k_{el} (h^{-1})	$t_{1/2}$ (h)	$AUC_{0\rightarrow 12h}$ (μM · h)	$AUC_{0\rightarrow\infty}$ (μM · h)	CL/F[a] (liters/h)
B	1.17 ± 0.44	7.22 ± 4.0	0.318 ± 0.093	2.39 ± 0.82	21.5 ± 13	22.5 ± 14	60.3 ± 46
C	1.58 ± 0.88	3.51 ± 1.9	0.197 ± 0.054	3.80 ± 1.2	12.9 ± 5.6	14.1 ± 5.7	77.0 ± 49
D	1.00 ± 0.37	6.90 ± 3.8	0.274 ± 0.089	2.77 ± 0.82	19.7 ± 11	20.5 ± 11	63.6 ± 48
ANOVA effects							
Period	0.555	0.873	0.565	0.787	0.952	0.919	0.925
Order	0.887	0.703	0.624	0.810	0.476	0.457	0.036
Treatment	0.066	0.018	0.003	0.003	0.114	0.164	0.475
C vs B							
ANOVA		0.031	0.003	0.003			
Wilcoxon	NS[c]	0.003	0.01	0.015	0.008	0.019	0.028
D vs B							
ANOVA		NS	NS	NS			
Wilcoxon	NS	NS	NS	NS	NS	0.875	0.814
C vs D							
ANOVA		0.056	NS	0.039			
Wilcoxon	0.046	0.016	NS	NS	0.041	NS	NS

[a] CL/F, clearance/bioavailability.
[b] Order 1 versus order 2, $P = 0.089$.
[c] NS, not significant.

Delavirdine and N-DLV. Delavirdine and N-DLV pharmacokinetic parameters according to study treatment are listed in Tables 2 and 3, respectively. Mean plasma concentration-versus-time profiles are graphically depicted in Fig. 1 and 2. Concomitant administration of delavirdine with didanosine (treatment C) significantly reduced the C_{max} of delavirdine compared with administration of delavirdine alone (treatment B) or delavirdine followed by didanosine (treatment D). Furthermore, both the k_{el} and terminal half-life ($t_{1/2}$) indicated prolonged elimination of delavirdine with treatment C relative to treatment B. Although no significant differences in $AUC_{0\rightarrow 12h}$ and $AUC_{0\rightarrow\infty}$ were detected across the three study treatments by use of ANOVA, pairwise comparisons done by using the Wilcoxon signed rank test indicated that treatment B resulted in reduced exposure to delavirdine relative to treatment B. When individual subject values were examined, subjects 3 and 12 were the only subjects in whom the $AUC_{0\rightarrow\infty}$ value for treatment C was higher than those for treatments B and D (by 11 and 52%, respectively.) (For clearance, an order effect was detected; however, pairwise comparison via Bonferroni's test did not indicate significance with regard to various orders of delavirdine study treatments.)

With regard to N-DLV, there were seven instances in which PCNONLIN could not estimate a terminal elimination phase.

TABLE 3. N-DLV pharmacokinetic parameters determined for treatments B, C, and D

Treatment or statistical test	Mean value for N-DLV ± SD or *P* value					Mean N-DLV/DLV $AUC_{0\rightarrow 12h}$ ratio ± SD or *P* value
	T_{max} (h)	C_{max} (μM)	k_{el} (h^{-1})	$t_{1/2}$ (h)	$AUC_{0\rightarrow 12h}$ (μM · h)h)	
B	1.29 ± 0.33	3.78 ± 1.3	0.222 ± 0.038	3.20 ± 0.55	19.4 ± 9.4	1.10 ± 0.52
C	2.13 ± 0.83	2.49 ± 1.1	0.153 ± 0.049	5.10 ± 2.0	14.4 ± 7.6	1.21 ± 0.49
D	1.17 ± 0.33	4.01 ± 1.43	0.179 ± 0.037	4.0 ± 0.78	19.2 ± 7.3	1.34 ± 1.0
ANOVA effects						
Period	0.498	0.747	0.670	0.697	0.847	0.891
Order	0.692	0.502	0.008[b]	0.011[b]	0.510	0.120
Treatment	<0.001	0.014	0.006	0.016	0.252	0.708
C vs B						
ANOVA	0.002	0.059	0.005	0.014		
Wilcoxon	0.016	0.002	0.046	0.046	0.003	NS[c]
D vs B						
ANOVA	NS	NS	NS	NS		
Wilcoxon	NS	NS	0.043	0.043	0.638	NS
C vs D						
ANOVA	<0.001	0.02	NS	NS		
Wilcoxon	0.01	0.005	NS	NS	0.019	NS

[a] Not including the seven cases in which terminal elimination could not be estimated.
[b] Order 3 versus order 1, $P \leq 0.038$.
[c] NS, not significant.

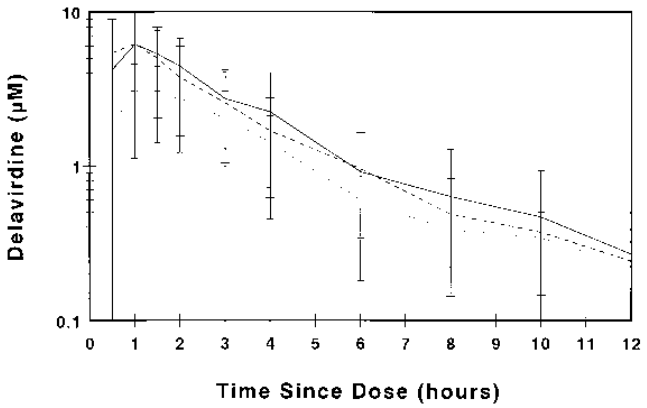

FIG. 1. Mean plasma concentration-versus-time curves for delavirdine taken alone (——), together with (·····), and 1 h before (– – – – –) didanosine.

Concurrent administration of delavirdine and didanosine significantly delayed the appearance of N-DLV and reduced C_{max} relative to treatments B and D. Similar to delavirdine, significant differences were not identified across study treatments by ANOVA, but Wilcoxon signed rank testing indicated that N-DLV exposure was reduced with treatment C compared with both treatments A and D. When the extent of metabolism (as indicated by the $AUC_{0\rightarrow\infty}$ ratio for N-DLV and delavirdine) was examined, no difference among the study treatments was observed. (An order effect was seen for N-DLV k_{el} and $t_{1/2}$, such that order 3 was significantly different from order 1.)

Didanosine. The didanosine pharmacokinetic parameters are listed in Table 4, and the mean plasma concentration-versus-time plot is depicted in Fig. 3. Subject 9 appeared to be an outlier from the remainder of the study subjects, having significantly lower exposures with treatments A and D (plasma concentrations and $AUC_{0\rightarrow\infty}$, which were below the 95% confidence interval for all overall values [data not shown]). Although the statistical analysis was unaffected by exclusion of subject 9, inclusion of this subject contributed to the variability of the pharmacokinetic parameters. When administered alone, didanosine was rapidly absorbed. There was a trend towards slower absorption when didanosine was administered with delavirdine, but statistical significance was not achieved. C_{max} was reduced with both treatments C and D relative to treatment A. The adjustment of $AUC_{0\rightarrow\infty}$ values for measurable didanosine at baseline resulted in a 1 to 2% reduction for most subjects, with the exception of subject 6, in whom an unusually high didanosine C_{0h} of 1.5 μM was noted. Adjustment of AUC for the C_{0h} for subject 6 in treatment A reduced the AUC by ≈50%, although both adjusted and unadjusted values were within the 95% confidence interval of the overall $AUC_{0\rightarrow\infty}$ values. Since no deviations from the protocol could be identified, the adjusted $AUC_{0\rightarrow\infty}$ value was included in the mean values reported in Table 4 and in the statistical analysis. The overall results were not changed when the statistical analyses were performed without adjustment of the $AUC_{0\rightarrow\infty}$ for subject 6 given treatment A. Concurrent administration of delavirdine with didanosine significantly reduced the $AUC_{0\rightarrow\infty}$, but the clearance of an orally administered dose was not statistically significantly different.

DISCUSSION

Combination regimens are being used more frequently in the treatment of HIV infection (3), and several studies have shown benefits to several combinations of antiretroviral therapies (5, 8, 13, 14, 25). The clinical use of NNRTIs as a class of antiretroviral drugs is limited by rapid development of resistance during monotherapy (19–24). Delavirdine is currently under clinical evaluation as a component of combination therapy with the nucleoside analogs zidovudine and/or didanosine (9). *In vitro* studies have shown that combinations have synergistic activity against HIV-1 (4). Since concomitant delavirdine and didanosine therapy is being used in these protocols, we conducted the present study to evaluate the potential for a pharmacokinetic interaction between these two agents.

The pharmacokinetic parameters for didanosine during treatment A (didanosine alone) agree with previously published studies done with available formulations of didanosine (2, 18). Concurrent administration of delavirdine appeared to have an effect on the pharmacokinetics of didanosine absorption and the AUC, with the didanosine exposure reduced by 10 to 30%. These effects were not observed when delavirdine was administered 1 h prior to didanosine. Since delavirdine has been found to reduce the minimum gastric pH from 4.7 ± 1.2 to 3.5 ± 1.2 among subjects with spontaneous gastric hypoacidity (29), increased acidity might facilitate the gastric degradation of didanosine. Alternatively, delavirdine may alter gastric emptying, competitively inhibit didanosine absorption, or enhance the metabolism of didanosine. Given the variability in exposure to didanosine from fixed doses of 200 mg every 12 h (2, 16, 18), the delavirdine-associated reduction in didanosine exposure determined in this study is unlikely to be clinically significant.

With regard to delavirdine, didanosine reduced the C_{max} by 30 to 60% relative to delavirdine given alone and delavirdine given 1 h prior to didanosine. It is interesting that the terminal $t_{1/2}$ of delavirdine was prolonged with concurrent administration of didanosine, likely indicating prolonged absorption; however, the time to maximum concentration of the drug in serum (T_{max}) was not significantly different. Although not different according to ANOVA, concurrent administration of didanosine was associated with reduced exposure to delavirdine relative to delavirdine given alone. Interestingly, there was one subject who had elevated delavirdine exposure during concurrent administration with didanosine. Delavirdine given 1 h before didanosine was no different from delavirdine given alone, suggesting that coadministration of these two drugs does not result in diminished absorption of either drug, provided that delavirdine is given 1 h before didanosine. Similar trends were apparent with N-DLV, although the extent of metabo-

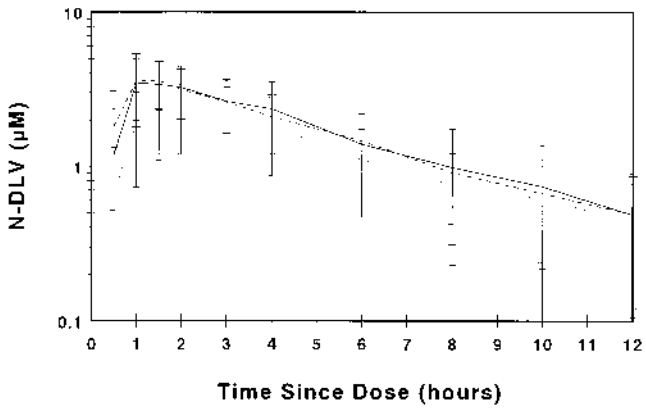

FIG. 2. Mean plasma concentration-versus-time curves for N-DLV taken alone (——), together with (·····), and 1 h before (– – – – –) didanosine.

TABLE 4. Didanosine pharmacokinetic parameters determined for treatments A, C, and D[a]

Treatment or statistical test	Mean value for didanosine ± SD or *P* value					
	T_{max} (h)[b]	C_{max} (μM)[b]	k_{el} (h^{-1})	$t_{1/2}$ (h)	$AUC_{0\rightarrow\infty}$ (μM · h)	CL/F[c] (liters/h)
A	0.583 ± 0.20	4.65 ± 2.0	0.440 ± 0.14	1.79 ± 0.77	7.93 ± 3.9	137 ± 79
C	0.773 ± 0.34	3.22 ± 0.59	0.417 ± 0.11	1.81 ± 0.71	6.54 ± 2.3	142 ± 42
D	0.778 ± 0.26	4.63 ± 1.3	0.437 ± 0.06	1.61 ± 0.22	7.94 ± 4.8	169 ± 189
C vs A; Wilcoxon	0.059	0.008	0.505	0.638	0.05	0.367
D vs A; Wilcoxon	0.102	0.678	0.583	0.814	0.875	0.638
C vs D; Wilcoxon	1.00	0.015	0.875	0.695	0.158	0.182

[a] C_{max} and $AUC_{0\rightarrow\infty}$ for two subjects receiving 125 mg of didanosine were normalized to a 200-mg dose.
[b] Data from four instances in which plasma sample collection deviated from the protocol were excluded.
[c] CL/F, clearance/bioavailability.

lism, as indicated by the N-DLV/delavirdine AUC ratio was unchanged among the various study treatments.

A study conducted by the manufacturer of delavirdine has demonstrated a 50% reduction in the delavirdine C_{max} and $AUC_{0\rightarrow\infty}$ when single 300-mg doses were administered with antacids (6). By extension, other medications which elevate the gastric pH, such as H_2 antagonists (i.e., cimetidine, ranitidine, and famotidine) and proton pump inhibitors (i.e., omeprazole), would be expected to reduce delavirdine absorption. Furthermore, spontaneous gastric hypoacidity has been reported among patients with AIDS, but the prevalence of this condition remains controversial (17, 26, 27, 30). The pathogenetic mechanism for this gastric hypoacidity is unknown. We have found that ≈20% of the HIV-infected subjects in our immunodeficiency clinic have gastric hypoacidity (mean gastric pH, ≥3), which may be related to coinfection with *Helicobacter pylori* (27, 28). Therefore, our observation that an elevated gastric pH results in reduced delavirdine absorption may have important implications for the chronic oral administration of delavirdine.

The results of our study support the theory that delavirdine absorption is impaired when the gastric pH is elevated by concurrent didanosine administration. Although the gastric pH was not monitored in our patients, we have found that the same didanosine dose and formulation increase the gastric pH to >9 (unpublished data). Although the duration of elevations in gastric pH due to didanosine were not determined, overnight fasting was sufficient to return the gastric pH to the baseline in most subjects. Delavirdine solubility decreases ≈200-fold when the pH is increased from 2 to 7.5 *in vitro* (5a), possibly accounting for the decrease in the delavirdine AUC *in vivo*. Although the precise anatomic site of delavirdine absorption is unknown, an acidic gastric pH would theoretically improve aqueous solubility, thereby improving absorption in either the stomach or small intestine. The lack of an intravenous preparation precludes making distinctions between changes in bioavailability versus alterations in metabolism. The prolonged elimination of delavirdine may have limited the impact of didanosine on delavirdine exposure. Although this single-dose study indicates reduced absorption of delavirdine when it is administered with didanosine, knowledge of the impact of didanosine on the steady-state pharmacokinetics of delavirdine is required before specific conclusions can be reached with regard to the importance of separating the administration times of these two antiretroviral agents during chronic therapy. However, preliminary results of a steady-state pharmacokinetic study of this combination suggest that although delavirdine exposure with chronic administration of didanosine with delavirdine may be lower than that achieved with separate administration, the difference in the clearance of an orally administered dose was not statistically significant (7).

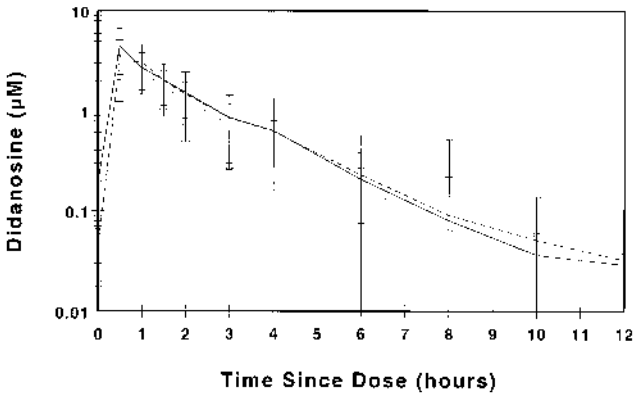

FIG. 3. Mean plasma concentration-versus-time curves for didanosine taken alone (——), together with (·····), and 1 h before (– – – – –) didanosine.

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