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Didanosine Reduces Atevirdine Absorption in Subjects with Human Immunodeficiency Virus Infections

GENE D. MORSE,[1,2]* MARGARET A. FISCHL,[3] MARK J. SHELTON,[1] MARIE T. BORIN,[4] MARY R. DRIVER,[4] MARY DEREMER,[1] KELLY LEE,[1] AND CHARLES P. WAJSZCZUK[4]

Laboratory for Antiviral Research, Department of Pharmacy Practice,[1] and Department of Medicine,[2] State University of New York at Buffalo, Buffalo, New York; Department of Medicine, University of Miami School of Medicine, Miami, Florida[3]; and The Pharmacia & Upjohn Company, Kalamazoo, Michigan[4]

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Atevirdine is a nonnucleoside reverse transcriptase inhibitor with in vitro activity against human immunodeficiency virus type 1 and is currently in phase II clinical trials. Atevirdine is most soluble at a pH of <2, and therefore, normal gastric acidity is most likely necessary for optimal bioavailability. Because of the rapid development of resistance in vitro, atevirdine is being evaluated in combination with didanosine and/or zidovudine in both two- and three-drug combination regimens. To examine the influence of concurrent didanosine (buffered tablet formulation) on the disposition of atevirdine, 12 human immunodeficiency virus type 1-infected subjects (mean $CD4^+$ cell count, 199 cells per mm^3; range, 13 to 447 cells/mm^3) participated in a three-way, partially randomized, crossover, single-dose study to evaluate the pharmacokinetics of didanosine and atevirdine when each drug was given alone (treatments A and B, respectively) versus concurrently (treatment C). Concurrent administration of didanosine and atevirdine significantly reduced the maximum concentration of atevirdine in serum from 3.45 ± 2.8 to 0.854 ± 0.33 μM ($P = 0.004$). Likewise, the mean atevirdine area under the concentration-time curve from 0 to 24 h after administration of the combination was reduced to 6.47 ± 2.2 μM · h ($P = 0.004$) relative to a value of 11.3 ± 4.8 μM · h for atevirdine alone. Atevirdine had no statistically significant effect on the pharmacokinetic parameters of didanosine. Concurrent administration of single doses of atevirdine and didanosine resulted in a markedly lower maximum concentration of atevirdine in serum and area under the concentration-time curve, with a minimal effect on the disposition of didanosine. It is unknown whether an interaction of similar magnitude would occur under steady-state conditions; thus, combination regimens which include both atevirdine and didanosine should be designed so that their administration times are separated. Since the duration of the buffering effect of didanosine formulations is unknown, atevirdine should be given prior to didanosine.

Atevirdine is a bisheteroarylpiperazine nonnucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against human immunodeficiency virus type 1 (HIV-1) at nanomolar concentrations (27, 32). It is highly protein bound (~98%) and undergoes capacity-limited hepatic metabolism (6, 28). Since HIV-1 has been noted to develop rapid in vitro and in vivo resistance to other NNRTIs (i.e., nevaripine and pyridinone) (11, 13, 18–21, 23–26, 29). NNRTIs are primarily being investigated in combination regimens with nucleoside analogs, such as zidovudine, didanosine, or zalcitabine (4, 12). These combinations have demonstrated additive to synergistic activity in vitro against clinical isolates of HIV-1 (5). Atevirdine is under clinical investigation in protocols conducted by the manufacturer and the AIDS Clinical Trials Group (protocols 187 and 199). These studies are evaluating the activity of atevirdine as a component of two- and three-drug combination regimens, along with zidovudine and/or didanosine or zalcitabine. Because of the acid lability of didanosine, oral dosage forms contain various buffers to prevent degradation in the acidic gastric milieu (3, 31). Since the solubility of atevirdine decreases with increasing pH (unpublished data), the absorption of atevirdine may be potentially reduced when it is administered with or soon after didanosine. The present study was undertaken to determine the effects of single, concurrent doses of atevirdine and didanosine on the disposition of each drug in subjects previously stabilized on didanosine.

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MATERIALS AND METHODS

The trial described here was an open-label, single-dose, pharmacokinetic study in 12 HIV-1-infected individuals between the ages of 18 and 55 years who were previously stabilized on didanosine monotherapy. All subjects had documented HIV-1 infection and a $CD4^+$ lymphocyte count of <500 cells per mm^3 within 30 days of entry into the study. In addition, the subjects had a complete medical history, physical examination with vital signs, and a resting 12-lead electrocardiogram during the screening period. All subjects met the following laboratory inclusion criteria: hemoglobin, >9.5 g%; absolute neutrophil count, >1,000/mm^3; platelet count, >100,000/mm^3; serum creatinine level of <1.6 mg/dl or estimated creatinine clearance of >50 ml/min determined by the standard formula, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels <2.5 times the upper limit of normal; bilirubin, <2.5 mg/dl; a negative urine drug screen for drugs of abuse; and no evidence of active substance abuse. The subjects agreed to abstain from alcohol for 48 h prior to the beginning of the study and until the final blood sample was drawn. Subjects were not eligible for participation in the study if they had one or more of the following exclusion criteria: clinically significant cardiovascular, renal, hepatic, pulmonary, endocrine, hematologic, vascular, or collagen disease; any acute medical problems requiring hospitalization; neurologic or psychiatric disorders which could impair subject compliance; use of any other investigational agents in the 15 days prior to the study; receipt of any known hepatic enzyme-inducing or -inhibiting agents or anticholinergic compounds for 30 days prior to the study period; use of pharmaceutical agents which may increase gastric pH (antacids, H_2-antagonists, proton pump inhibitors); prior history of hypersensitivity to piperazine-type drugs; or pregnancy or breast-feeding. The protocol was approved by the Institutional Review Board at the University of Miami School of Medicine, and informed consent was obtained prior to entry into the study.

* Corresponding author. Mailing address: 247 Cooke Hall, Department of Pharmacy Practice, State University of New York at Buffalo, Amherst, NY 14260. Phone: (716) 645-3635. Fax: (716) 645-2001.

TABLE 1. Demographic characteristics of patients participating in a pharmacokinetic study of atevirdine and didanosine

Subject no	Sex[a]	$CD4^+$ count (no. of cells/mm^3)	Age (yr)	Race[b]	Wt (kg)	Body frame size[c]	Didanosine dose (mg)
01	F	59	35	W	48.6	S	125
02	F	13	27	W	64.5	M	200
03	F	406	43	B	63.2	M	200
04	M	373	38	W	100.9	L	200
05	F	113	36	W	60.0	M	200
06	M	248	40	W	75.5	M	200
07	M	245	47	H	84.5	M	200
08	M	447	30	W	75.5	M	200
09	M	29	42	W	76.8	L	200
10	M	46	35	H	65.9	M	200
11	M	170	32	W	67.9	S	200
12	M	233	47	W	85.5	L	200
Mean		199	37.7		72.4		
SD		152	6.4		13.8		

[a] F, female; M, male.
[b] W, white; B, black; H, Hispanic.
[c] S, small; M, medium; L, large, according to the Metropolitan Life Insurance Co. (19a).

The study was conducted on 3 sequential days in a clinic setting, with the subjects returning on the morning of each study treatment. Subjects fasted from midnight before treatment until 4 h after dosing during each study treatment. All study meals were isocaloric (regular diets) and were consumed over a 30-min period. Doses were administered by clinic personnel. All but one subject received 200 mg of didanosine as the tablet formulation (given as two tablets) in the first study period. One subject received 125 mg because of a body weight of <50 kg. Afterward, the subjects were randomized to receive either 600 mg of atevirdine alone (treatment B) or concomitant doses of atevirdine and didanosine (treatment C). Each study treatment was separated by 1 day.

Whole-blood samples (5 ml) were withdrawn from an indwelling intravenous canula and placed into heparin-containing tubes at the following times following drug administration: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h. Additional samples were collected at 16 and 24 h after the administration of atevirdine. Plasma was harvested by centrifuging the specimens at 2,000 × *g* for 10 min. The upper plasma layer was then transferred to storage vials, and the vials were frozen at −20°C. The samples were then transported by overnight delivery to the pharmacology laboratory for drug assay.

Drug analysis. (i) Atevirdine. The concentrations of atevirdine and its *N*-dealkylated metabolite (N-ATV) were quantitated in human plasma by a method developed and validated at the Upjohn Company (Kalamazoo, Mich.) (14). Following extraction from plasma by protein precipitation with an acetonitrile-containing internal standard (U-88352; Pharmacia & Upjohn Co., Kalamazoo, Mich.), the samples were directly injected onto the chromatographic system. The compounds were measured by fluorescence detection with excitation at 295 nm and emission filtration at 418 nm. The mobile phase consisted of 20 mM ammonium acetate (pH 4.0) and acetonitrile (52:48). All calculations were performed by using SAS version 6.07 software on an International Business Machines mainframe computer. Peak heights for atevirdine, N-ATV, and internal standard were regressed against concentration by least-squares analysis according to a weighting scheme ($1/concentration^2$) to derive a calibration curve. All calibration curves were required to be linear (i.e., correlation coefficient of ≥0.995). The following two different calibration curves were used: 500 to 25,000 and 31.25 to 1,000 ng/ml. The highest concentration curve was typically used to determine the initial concentrations in the subjects. Any concentrations which fell below 500 ng/ml were reanalyzed by using the lower curve. The lower limits of quantitation were 0.0824 and 0.0889 μM for atevirdine and N-ATV, respectively. Intra-assay variations for atevirdine and N-ATV were ≤4% at all quality control concentrations. Interassay variations for atevirdine were 5, 3, and 6% at 100, 2,000, and 20,000 ng/ml, respectively. For N-ATV, interassay variations were 5, 7, and 4% at the concentrations identical to those for atevirdine, respectively. In vitro studies indicate no interference by didanosine on the determination of atevirdine or N-ATV (data not shown).

(ii) Didanosine. Plasma didanosine concentrations were measured by a radioimmunoassay with reagents purchased from Sigma Chemical Co. (St. Louis, Mo.) (8). The methodology used a double-antibody measurement principle, with ^3H-didanosine used as the tracer. Standard concentrations of 0.4, 0.8, 1.6, 2.5, 4, 10, 15, 25, 50, and 100 ng/ml were used. Quality controls at 2.0, 5.0, 8.0, and 30 ng/ml were evaluated. Unknown samples were assayed by using various dilutions from 1:10 to 1:100 in buffer. The lower and upper limits of quantitation were 0.00847 and 0.212 μM, respectively. Radioactivity was measured in a Wallac 1409 DSA-based liquid scintillation counter (Wallac, Gaithersburg, Md.). A four-parameter equation was used to fit the standard curve by using the RiaCalc.LM version 2.65 software package (Wallac). Variation was typically 3 to 10%, with larger variation seen at the highest standard concentration. Intra-assay variation ranged from 0.3 to 3% at 30 ng/ml. Variations were 10, 8, 17, and 9% at 2.0, 5.0, 8.0, and 30 ng/ml, respectively. In vitro studies indicated no interference by atevirdine or N-ATV on the didanosine assay (data not shown).

Data analysis. Pharmacokinetic analysis was accomplished with PCNONLIN software (SCI Software, Lexington, Ky.) by noncompartmental methods. The elimination rate constant (k_{el}) was determined from the slope of the terminal phase of the concentration-versus-time profile by least-squares regression. The elimination half-life ($t_{1/2}$) was calculated according to the equation $t_{1/2} = 0.693/k_{el}$. The area under the curve (AUC) was estimated by the trapezoidal rule and was then used to calculate oral clearance (CL) by the following equation: CL/F = dose/AUC, where F is bioavailability. For didanosine, the AUC from time zero to infinity ($AUC_{0-\infty}$) was calculated by extrapolating the AUC from time zero to 12 h (AUC_{0-12}) to infinity by the following equation: $AUC_{0-\infty} = AUC_{0-12} + C_{12}/k_{el}$ (where C_{12} is the concentration of drug at 12 h). Because of the nonlinear nature of atevirdine pharmacokinetics, the AUC from 0 to 24 h (AUC_{0-24}) was reported for atevirdine and N-ATV as an indicator of exposure and the elimination rate parameters (k_{el} and $t_{1/2}$) were not reported. The ratios of the AUC for N-ATV:AUC for atevirdine were calculated for each study subject and are reported as an indicator of the extent of metabolism. Because of the nonrandomized order of didanosine administration, didanosine parameters were compared by the Wilcoxon signed-rank test. Since subjects were randomized as to the order in which they received atevirdine, the pharmacokinetic parameters for atevirdine and N-ATV were compared by a paired Student *t* test (with the exception of the time to the maximum concentration of drug in serum [T_{max}], which was compared by the Wilcoxon signed-rank since T_{max} is a noncontinuous variable.) The mean difference in each pharmacokinetic parameter was determined and is reported along with 95% confidence interval around that difference.

RESULTS

Subject demographics are summarized in Table 1. The subjects enrolled in the study had a mean $CD4^+$ lymphocyte count of 199 ± 153 cells per mm^3. Four of the 12 subjects were female, and the mean age was 33.7 ± 6.4 years.

Atevirdine. The mean plasma atevirdine concentrations when the drug was given alone (treatment B) and concomitantly with didanosine (treatment C) are provided in Fig. 1. The variability in concentrations in plasma at each time point, expressed as the coefficient of variation, ranged from 26 to 100%. The mean pharmacokinetic parameters are provided in Table 2. Atevirdine was rapidly absorbed during both treatments (T_{max} = 0.708 ± 0.33 h for treatment B and 0.958 ± 0.81 h for treatment C; P = 0.334), but the maximum concentration of drug in serum (C_{max}) was significantly reduced approximately fourfold (from 3.45 ± 2.8 to 0.854 ± 0.33 μM; P = 0.004) during treatment C. The AUC_{0-24} during treatment C was significantly lower (by approximately 50%) compared with

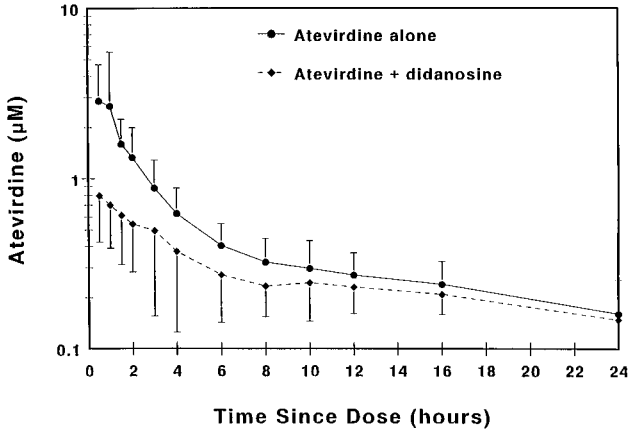

FIG. 1. Atevirdine plasma concentration-versus-time curves when atevirdine was given alone and together with didanosine.

TABLE 2. Pharmacokinetic parameters for atevirdine and the N-ATV metabolite in plasma

Treatment	Atevirdine			N-ATV			
	T_{max} (h)	C_{max} (μM)	AUC_{0-24} (μM · h)	T_{max} (h)	C_{max} (μM)	AUC_{0-24} (μM · h)	AUC ratio[a]
B	0.708 ± 0.33	3.45 ± 2.8	11.3 ± 4.8	1.38 ± 1.0	5.87 ± 9.6	23.5 ± 9.2	2.27 ± 1.0
					3.13 ± 1.2[b]	22.7 ± 9.2[b]	2.34 ± 1.1[b]
C	0.958 ± 0.81	0.854 ± 0.33	6.47 ± 2.2	2.50 ± 2.7	0.945 ± 0.43	9.26 ± 5.6	1.49 ± 0.84
B-C	−0.25–0.78	2.6 ± 2.6	4.8 ± 4.1	−1.1 ± 2.6	4.9 ± 9.6	14 ± 9.0	0.78 ± 0.72
					2.3 ± 1.1[b]	13 ± 8.2[b]	0.75 ± 0.75[b]
95% Confidence interval	−0.69–0.19	1.1–4.1	2.5–7.1	−2.6–0.4	0.66–10	8.9–19	0.37–1.2
					1.5–2.9[b]	8.4–18[b]	0.33–1.2[b]
P value	0.317[c]	0.006[d]	0.002[d]	0.182[c]	0.105[d]	<0.001[d]	0.003[d]
					<0.001[b,d]	<0.001[b,d]	0.008[b,d]

[a] Ratio of AUC for N-ATV to AUC for atevirdine.
[b] Value when outlier (subject 5, treatment B) was excluded.
[c] Wilcoxon signed-rank test.
[d] Paired Student *t* test.

that during treatment B (11.3 ± 4.8 versus 6.47 ± 2.2 μM · h; $P = 0.004$). N-ATV followed a similar pattern, although statistical significance was achieved for C_{max} only when one outlier was deleted from the analysis. The value for C_{max} for subject 5 receiving treatment B (36 μM at 1 h) was determined to be an outlier, since this value was approximately 10-fold greater than the mean value for the remainder of the subjects receiving treatment B (2.77 ± 1.29 μM). The extent of metabolism, as indicated by the AUC ratios, was significantly reduced with treatment C relative to that with treatment B. There were no significant differences in any of the pharmacokinetic parameters between subjects with regard to the sequence of treatments B and C (i.e., no difference between subjects receiving treatment B and then treatment C versus those receiving treatment C and then treatment B).

Didanosine. The mean plasma didanosine concentrations during treatments A (didanosine alone) and C (concomitant didanosine and atevirdine) are provided in Fig. 2, whereas the mean pharmacokinetic parameters are summarized in Table 3. Didanosine was rapidly absorbed during both treatments; T_{max} occurred at 0.5 h in all instances. C_{max} was similar with both treatments, although there appeared to be more variability in C_{max} with treatment C. Although no significant differences were detected in didanosine pharmacokinetic parameters, there was a trend toward an increased CL for treatment C ($P = 0.06$).

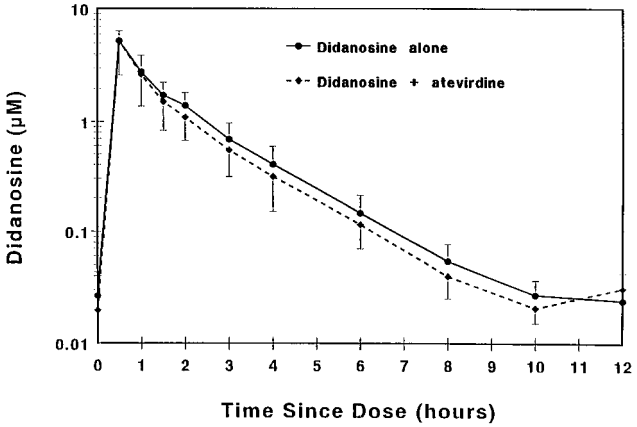

FIG. 2. Didanosine plasma concentration-versus-time curves when didanosine was given alone and together with atevirdine.

DISCUSSION

The NNRTIs as an antiviral category have potent in vitro activity against HIV-1 (7, 9, 10). The potentially synergistic activity between atevirdine and nucleoside analogs demonstrated in vitro has prompted current various phase II studies which compare atevirdine monotherapy with zidovudine or atevirdine-zidovudine combinations. In addition, two AIDS Clinical Trials Group protocols (protocols 187 and 199) have evaluated atevirdine alone and in combination with zidovudine, didanosine, and zalcitabine. The likelihood that atevirdine would be further investigated in combination with didanosine prompted the present pharmacokinetic interaction study.

Similar to single-dose studies of atevirdine given in a fasting state versus 10 min after the ingestion of an aluminum-magnesium hydroxide antacid suspension (2), both the C_{max} and AUC for atevirdine were reduced approximately two- to threefold in the presence of didanosine. The exposure to N-ATV was also significantly reduced (≈50%) with concurrent administration of didanosine. Although reduced absorption may be difficult to distinguish from reduced metabolism in the absence of intravenous data, the extent of metabolism (as indicated by the ratios of the AUC for N-ATV/AUC for atevirdine) was also reduced during concurrent administration of atevirdine and didanosine. Thus, it is possible that didanosine may have inhibited the metabolism of atevirdine; however, a similar pattern was found in the atevirdine-antacid study mentioned earlier, suggesting a local reduction in solubility in the stomach. Although the gastric pH was not monitored in our subjects, administration of the same didanosine formulation and dose resulted in a gastric pH of >7 in a series of HIV-1-infected subjects without gastric achlorhydria ($n = 8$) prior to didanosine administration (unpublished data). In vitro studies indicate that atevirdine solubility decreases as the pH is increased from 1 to 7 (unpublished data). By extrapolation, it would seem plausible that other medications which elevate gastric pH, such as antacids, H_2-antagonists (i.e., cimetidine, ranitidine, and famotidine), and proton pump inhibitors (i.e., omeprazole) may also reduce atevirdine absorption, as has been found with ketoconazole (1, 17, 22). Spontaneous gastric hypoacidity has been reported among patients with HIV-1 infection, regardless of the $CD4^+$ cell count (16, 30). The pathogenic mechanism for the elevated gastric pH is unknown, but patients have been noted to have elevated circulating gastrin and reduced vitamin B_{12} absorption, suggesting a reduced functional parietal cell mass (15, 16, 30). Therefore, our ob-

TABLE 3. Pharmacokinetic parameters for didanosine administered alone and together with atevirdine

Treatment	T_{max} (h)	C_{max} (μM)	k_{el} (h^{-1})	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μM · h)	CL/*F* (liters/h)
A didanosine alone	0.5 ± 0.0	5.27 ± 1.12	0.467 ± 0.099	1.55 ± 0.36	7.78 ± 2.1	114 ± 36
C	0.5 ± 0.0	5.35 ± 2.65	0.471 ± 0.081	1.52 ± 0.31	7.00 ± 2.7	131 ± 41
A-C	0.00 ± 0.00	−0.083 ± 2.2	−0.005 ± 0.1	0.034 ± 0.353	0.77 ± 1.8	−18 ± 25
95% Confidence interval	0–0	−1.3–1.3	−0.062–0.52	−0.17–0.23	−0.28–1.8	−32–−4
P value[a]	1.00	0.638	0.530	0.695	0.158	0.060

[a] Wilcoxon signed-rank test.

servation that an elevated gastric pH results in reduced atevirdine absorption may have important implications for the chronic oral administration of atevirdine in HIV-1-infected patients.

Another aspect of our data is the consideration of the profiles of the concentration in plasma which result when atevirdine and didanosine are taken together. Prior in vitro data have revealed that additive antiviral activity was attained by using equimolar combinations of these two agents at concentrations of from 0.01 to 2.0 μM (5). In our subjects these concentrations were exceeded for up to 12 and 8 h, respectively. In current clinical trials, atevirdine is given every 8 h and didanosine is given every 12 h. Although trough concentrations of didanosine in plasma are not expected to accumulate during chronic dosing, atevirdine is expected to demonstrate saturable metabolism, and this may result in even more prolonged exposure to this agent, as well as prolongation of the interval over which synergistic drug concentrations are maintained. Although the concentrations of didanosine in plasma may decrease below 0.01 μM in some patients, the prolonged intracellular $t_{1/2}$ of its active anabolite, dideoxyadenosine triphosphate, will likely provide a prolonged period of reverse transcriptase inhibition from the didanosine component of the regimen.

In summary, the results of the present study of the interaction of single doses of atevirdine and didanosine indicate that the buffered dosage form of didanosine reduces atevirdine absorption when the two agents are administered concurrently. While these findings have immediate clinical relevance for the medication administration schedule for protocols which will evaluate the efficacy of this regimen, a study of the impact of didanosine on the steady-state pharmacokinetics of atevirdine is required before specific conclusions can be reached with regard to the importance of separating the administration times for these two antiretroviral agents. Current recommendations are to separate atevirdine from didanosine administration by 1 h, and long-term studies of the combination are in progress.

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