Safety and Pharmacokinetics of 5-Chloro-2',3'-Dideoxy-3'-Fluorouridine (935U83) following Oral Administration of Escalating Single Doses in Human Immunodeficiency Virus-Infected Adults

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5-Chloro-2',3'-dideoxy-3'-fluorouridine (935U83) is a nucleoside analog reverse transcriptase inhibitor that has demonstrated selective anti-human immunodeficiency virus (HIV) activity in vitro and favorable safety profiles in monkeys and mice. A phase I study was conducted to evaluate the safety and pharmacokinetics of six escalating single oral doses of 935U83 in 12 HIV-infected adults. The effect of a high-fat meal on the oral bioavailability of 935U83 was also assessed. The volunteers enrolled had CD4⁺ cell counts ranging from <50 to 753 cells per mm³ (median, 198). In the dose range of 100 to 1,500 mg, 935U83 was well tolerated by all subjects with no drug-related adverse events reported. No significant clinical or laboratory abnormalities were observed throughout the study. 935U83 was rapidly and well absorbed following oral administration with peak plasma concentrations ($C_{\max}$) occurring at 0.8 to 1.3 h postdosing. Mean $C_{\max}$ and $AUC_{0-\infty}$ values of 935U83 were nearly dose proportional in the 100- to 1,500-mg dose range (from 2.4 to 30 $\mu\text{g/ml}$ and from 3.4 to 59 h $\cdot$ $\mu\text{g/ml}$, respectively). Elimination of 935U83 from the plasma was rapid, with an apparent half-life of 1.3 to 1.7 h which was independent of the dose level. Administration of 935U83 with a high-fat meal decreased the rate of 935U83 absorption (mean $C_{\max}$ decreased by ~50% and mean time to $C_{\max}$ increased by ~1 h) but did not affect the extent of oral bioavailability ($AUC_{0-\infty}$) of 935U83. The 5'-*O*-glucuronide conjugate was the principal metabolite of 935U83 and was present in the plasma of all volunteers at concentrations lower than 935U83. The molar $AUC_{0-\infty}$ ratio (935U83 glucuronide to the parent compound) was similar across all dose levels (mean, 21 to 27%). At least 60% of the 935U83 dose was absorbed, and approximately an equal percentage of the dose (~30%) was excreted as unchanged 935U83 and as 935U83 glucuronide. Systemic exposure to 935U83 at levels exceeding its average in vitro antiretroviral 50% inhibitory concentration (~0.5 $\mu\text{g/ml}$ or 1.8 μM) can be achieved after a single oral dose.

The recently approved combination therapy of zidovudine and lamivudine (3TC) has proven the value of combined anti-human immunodeficiency virus (HIV) therapy (1, 8), and many new anti-HIV agents are now being developed for use in two- or three-drug combination therapy. Compound 935U83, 5-chloro-2',3'-dideoxy-3'-fluorouridine, is a synthetic pyrimidine nucleoside analog (see Fig. 1) that inhibits HIV type 1 (HIV-1) replication with low cytotoxicity in MT4 cells (human leukemic cell line transformed with human T-cell leukemia virus type 1), peripheral blood lymphocytes, and macrophages (5). Like zidovudine, 935U83 is phosphorylated in a stepwise manner to the 5'-triphosphate by cellular enzymes. The mechanism of 935U83's anti-HIV activity appears to be substrate inhibition of HIV reverse transcriptase by the triphosphate of 935U83. When tested in phytohemagglutinin-stimulated, normal human peripheral blood lymphocytes against fresh clinical isolates of HIV-1 obtained from zidovudine-naïve patients, 935U83 inhibited virus growth with an average 50% inhibitory concentration (IC_{50}) of 1.8 μM ; corresponding IC_{50} 's for zidovudine, ddI, and ddC were 0.23, 0.49, and 0.03 μM , respectively (5). 935U83 did not show reduced activity against

HIV strains that were resistant to zidovudine, ddI, ddC, lamivudine, nevirapine, and other nonnucleoside antiretroviral agents (5, 6). In addition, 935U83 in combination with several anti-HIV agents (3TC, ddI, ddC, and nevirapine) exhibited synergistic inhibition of HIV-1 strain IIIB in MT4 cells (6).

In preclinical studies, 935U83 has been shown to have minimal toxicity both in vitro (cytotoxic, cytogenetic, and mutagenic assays) and in animals (5). In monkeys dosed orally with up to 700 mg of 935U83 per kg per day for 6 months, the only possible drug-related finding was cataracts in 1 of 12 animals given an intermediate dose of 225 mg/kg/day. No lenticular changes were seen in monkeys given 75 or 700 mg/kg/day. After oral administration, 935U83 was rapidly and well absorbed, with an absolute bioavailability of 86% in mice and 60% in monkeys. 935U83 was primarily eliminated (unchanged) via urinary excretion, with 89 and 63% of the dose recovered in urine from mice and monkeys, respectively (5, 12). The principal metabolite of 935U83 identified in monkey urine (3.4% of the dose administered) was the 5'-*O*-glucuronide (Fig. 1).

The promising in vitro anti-HIV activity of 935U83 alone and in combination with other antiretroviral agents, along with limited toxicologic effects and desirable pharmacokinetic characteristics, has led to the clinical development of 935U83. The first phase I study, described in this report, was conducted to

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FIG. 1. Chemical structures of 935U83 ($M_r = 264.6$) (a) and its principal metabolite, 935U83-5'-glucuronide ($M_r = 440.8$) (b).

determine the safety and pharmacokinetics of single escalating oral doses of 935U83 in HIV-infected volunteers.

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MATERIALS AND METHODS

Study population. Male or female HIV-infected volunteers of any race, between 13 and 55 years of age, weighing within 10% of ideal body weight were eligible for enrollment. Written informed consent was obtained from all participants, and the study was approved by the Institutional Review Boards of the University of Pittsburgh Medical Center and Duke University Medical Center. Each center enrolled six patients. The volunteers had tested positive for antibody to HIV-1 or had clinical evidence of HIV infection as defined by the Centers for Disease Control HIV classification guidelines. Subjects were excluded from enrollment if they had a history of hepatitis or pancreatitis within the last 5 years, an estimated creatinine clearance (CL_{CR}) of ≤ 50 ml/min, a hemoglobin level of <11.0 g/dl (for men) or <10 g/dl (for women), a neutrophil count of $<1,500$ cells per mm^3 , a platelet count of $<100,000$ cells per mm^3 , or serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 3 times the upper normal limit. All prescription and over-the-counter medications were withheld for 48 h (or 24 h for antiretroviral agents) prior to dosing and during the day of 935U83 dosing.

Study design. This was a phase I, open-label, single-dose escalation study. Each volunteer received six single escalating oral doses of 935U83 separated by at least a 6-day washout interval between doses. The six doses of 935U83 administered sequentially were 100 (Period I), 300 (Period II), 300 (Period III), 600 (Period IV), 1,000 (Period V), and 1,500 mg (Period VI). During the two 300-mg dose periods, the effect of food (a high-fat meal) on the pharmacokinetics of 935U83 was assessed. The order in which the participants first received the 300-mg dose with food or after an overnight fast was determined by a randomization schedule. The study drug was supplied as 100-mg and 200-mg white, scored convex tablets by Wellcome Foundation Ltd., Dartford, United Kingdom. Each volunteer took the 935U83 doses (1 to 8 capsules) with 200 ml of water and fasted for another 3 h following each dose except when assigned to receive the dose with a standardized high-fat meal (2 eggs, 2 strips of bacon, 1 piece of toast with butter, 4 oz [1 oz = ca. 28 g] of hash brown potatoes, and 8 oz [1 oz = ca.

30 ml] of whole milk), which was consumed within 30 min following administration of the 300-mg dose.

Within 14 days of the first dose, volunteers underwent a screening evaluation, including a medical history, physical examination, and measurement of clinical laboratory parameters. Volunteers were admitted to the clinical research unit in the morning after an overnight fast (at least 8 h) and remained at the site until 24 h postdosing. Volunteers were instructed to return to the study site at least 6 days later to begin the next dosing period. Seven to 10 days after completing the last dosing period, volunteers returned for a follow-up examination similar to the screening evaluation.

Blood and urine samplings. Blood samples (3 ml each) were collected by venipuncture into heparin-containing Vacutainer tubes immediately prior to dosing and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 h following each dosing. Blood samples were kept at $4^\circ C$ upon collection and centrifuged within 1 h of collection to separate the plasma, which was stored frozen at $-40^\circ C$ until analyzed. Urine samples were collected prior to administration of the dose and over the intervals of 0 to 4, 4 to 12, and 12 to 24 h postdosing. During each interval, the collection container was refrigerated or kept on ice except during voiding. The total urine volume for each collection interval was measured, and a portion (10 ml) was stored frozen at $-40^\circ C$ until analyzed.

Safety evaluation. The safety-tolerability of single escalating doses of 935U83 was evaluated based on adverse experience reports, measurements of vital signs and clinical laboratory values, and results of physical examination. Study subjects were monitored carefully throughout each dosing period for adverse experiences. Vital signs (sitting blood pressure and sitting pulse), routine hematology (complete blood count with differential, mean corpuscular volume, and platelet count), serum chemistry (electrolytes, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and serum amylase) and urinalysis (dipstick for protein and blood) were evaluated at screening, during each dosing period, and at a follow-up visit.

Assays for plasma and urine samples. An isocratic reversed-phase high-performance liquid chromatographic-mass spectrometric method (LC-MS) was used for measuring plasma concentrations of 935U83 (7). Plasma concentrations of 935U83 glucuronide were determined indirectly after hydrolysis to 935U83 by using β -glucuronidase. Since the sensitivity of the mass spectrometer was not required for the analysis of urine samples, the following modifications to the LC-MS method were made to allow the use of UV detection at 275 nm. Urine samples (100 μ l), before and after treatment with β -glucuronidase, were combined with 25 μ l of internal standard (250 μ g/ml of the 5-bromo analog), a saturated solution of sodium chloride (0.9 ml), and acetonitrile (2 ml). The acetonitrile layer was then extracted by using an anionic solid-phase extraction procedure (7). Elution of 935U83 off the Inertsil ODS-2 analytical column (5 mm by 25 cm) was made by using a step gradient from 0.5% acetic acid containing 14% acetonitrile (4 min) to 57% acetonitrile (2 min) and then returning to initial conditions. The quantifiable range of 935U83 was between 4 and 3,100 ng/ml and between 1 and 500 μ g/ml for plasma and urine analyses, respectively. The bias and the intra- and interday variabilities, calculated from the control samples included with the analysis of the patient samples, were all less than 8% for both methods.

Pharmacokinetic analysis. Plasma concentration-time data of 935U83 and 935U83 glucuronide were analyzed using noncompartmental pharmacokinetic methods (9). C_{max} (peak concentration) and T_{max} (peak time) were obtained from direct inspection of the plasma concentration-time data. Estimate for $t_{1/2}$ (apparent half-life) was calculated as $\ln(2)/\lambda_z$, where λ_z is a first-order rate constant determined by the slope of the linear regression line of the apparent terminal linear portion of the log concentration versus time curve. AUC_{0-t} (area under the curve) was calculated by using the linear trapezoidal method from time zero to t , where t is the last time point with a measurable concentration of the compound of interest. $AUC_{0-\infty}$ was then determined as $AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration of the compound of interest. The apparent plasma clearance (CL/F) for 935U83 was calculated as dose divided by $AUC_{0-\infty}$ and then normalized to body weight.

The percentages of the dose recovered in urine as unchanged 935U83 and as 935U83 glucuronide were determined. Time-averaged renal clearances (CL_R) of 935U83 and its glucuronide were calculated as the cumulative amount of each compound recovered in the urine over the 24-h period divided by $AUC_{0-\infty}$ of the respective compound. Body weight-normalized CL_R values were compared with CL_{CR} which was estimated from serum creatinine (S_{CR}) measured at study entry and during each dosing period as follows (10): $CL_{CR} = BW \times (29.3 - 0.203 \times \text{age}) / (14.4 \times S_{CR})$ for male volunteers and $CL_{CR} = BW \times (25.3 - 0.175 \times \text{age}) / (14.4 \times S_{CR})$ for female volunteers, where BW is body weight in kilograms and units for age and S_{CR} are years and mg/dl, respectively.

Statistical analysis. Comparisons of λ_z , body weight-normalized CL/F , and dose-normalized C_{max} and $AUC_{0-\infty}$ values of 935U83 between the escalating doses administered under fasting conditions were performed by using analysis of variance (ANOVA). C_{max} , $AUC_{0-\infty}$, and CL/F values were compared by using log-transformed (base e) data. A 95% confidence interval (CI) was constructed for the parameter estimated at each dose level by using the least square mean (LSM) and standard error estimates from ANOVA. Comparison of T_{max} between doses was performed by using the Wilcoxon signed rank test. Regression analysis of $\ln(AUC_{0-\infty})$ versus $\ln(\text{dose})$ or $\ln(C_{max})$ versus $\ln(\text{dose})$ was performed to determine the correlations and to construct a 90% CI for the slope of

TABLE 1. Mean pharmacokinetic parameter estimates for 935U83 following single oral administration of 100- to 1,500-mg doses in HIV-infected volunteers^a

Dose (mg), exptl condition	$C_{\max}$ [$\mu\text{g/ml}$ (% CV)]	$T_{\max}$ [h (% CV)]	$\text{AUC}_{0-\infty}$ [h $\cdot$ $\mu\text{g/ml}$ (% CV)]	$t_{1/2}$ [h (% CV)]	CL/F [ml/min/kg (% CV)]
100, fasting	2.37 (32)	0.77 (45)	3.37 (21)	1.40 (8)	7.71 (26)
300, fasting	7.86 (25)	0.80 (52)	11.1 (16)	1.33 (8)	6.90 (20)
300, with food	4.35 (33)	1.98 (48)	10.3 (23)	1.26 (17)	7.65 (24)
600, fasting	12.3 (22)	1.14 (59)	21.9 (18)	1.28 (17)	7.03 (20)
1,000, fasting	19.0 (25)	1.32 (54)	37.2 (19)	1.45 (20)	6.93 (20)
1,500, fasting	30.5 (24)	1.27 (57)	59.0 (21)	1.68 (20)	6.61 (24)

^a $n = 12$ for the 100-mg dose; $n = 11$ for other doses. Values in parentheses are coefficients of variation (CV).

the regression line. ANOVA was also performed to compare $C_{\max}$ and $\text{AUC}_{0-\infty}$ between the 300-mg doses administered under fed and fasted conditions. A 90% CI was determined for the ratio of the parameter estimates (fed to fasted) by using the two one-sided t tests.

RESULTS

Volunteer demographics and characteristics. Eleven male (nine white, two black) volunteers and one female (white) volunteer participated in this study. Their ages ranged from 22 to 56 years (36 ± 11 , mean $\pm$ standard deviation), and they weighed between 59.9 and 78.0 (68.9 ± 5.9) kg. All volunteers had normal renal function; the estimated CL_{CR} ranged from 91.9 to 138.0 ml/min (98.6 ± 22.3 ml/min) at entry. CD4^+ cell counts ranged from <50 to 753 cells per mm^3 (median, 198 cells per mm^3) prior to study entry. Three individuals had AIDS (Center for Disease Control 1987 Surveillance Definition), three were symptomatic without AIDS, and six were asymptomatic. Eleven volunteers received all six doses of 935U83, and one volunteer withdrew from the study after the first dose for personal reasons.

Safety evaluation. Compound 935U83 was well tolerated in single oral doses up to 1,500 mg. Six adverse events were reported by four volunteers. None were serious, all were mild to moderate in intensity, and only two mild events were possibly attributable to 935U83. One volunteer developed anxiety, nervousness, and jitteriness for approximately 1 h after receiving the 1,500-mg dose of 935U83. The other volunteer had a 2-min episode of feeling flushed after the 1,500-mg dose. Both events resolved spontaneously without sequelae. Other adverse events that were judged by the investigators to be unrelated to 935U83 included headache, diarrhea, and dyspepsia. No laboratory abnormalities of grade 2 or greater (World Health Organization toxicity scale) were observed. No changes in hematologic parameters were observed. Four individuals had mild elevations in AST, ALT, or bilirubin (grade 1), all of which returned to baseline levels despite continued weekly doses of 935U83. The greatest elevations of AST, ALT, and bilirubin levels were less than twice the upper limit of normal in all cases.

Pharmacokinetic evaluation. Pharmacokinetic parameter estimates for 935U83 are listed in Table 1. Following oral administration, 935U83 was rapidly absorbed, achieving measurable plasma concentrations by the first sampling time (15 min). In general, plasma 935U83 concentrations fell below detectable levels (4 ng/ml) at or after 12 h postdosing. Mean plasma 935U83 concentration versus time profiles are depicted in Fig. 2 (100- to 1,500-mg doses under fasting conditions) and in Fig. 3 (300-mg dose with food). Peak 935U83 concentrations occurred between 0.25 and 3.0 h following dosing under fasting conditions and from 0.75 to 4.0 h when the dose was administered with a high-fat meal. The absorption characteristics of 935U83 within each individual between different doses were variable, with double peaks occurring especially at doses

of ≥ 600 mg. In addition, $T_{\max}$ was significantly longer at doses of $\geq 1,000$ mg than at doses of ≤ 300 mg ($P \leq 0.05$). When 935U83 was administered with a high-fat meal, peak 935U83 concentration was lower and occurred later (Fig. 3), with $T_{\max}$ increasing from 0.8 to ~ 2 h ($P < 0.01$).

Mean peak 935U83 concentrations increased nearly dose proportionally from 2.37 to 30.5 $\mu\text{g/ml}$ when the dose was increased from 100 to 1,500 mg (fasted). Based on LSMs and 95% CIs determined by ANOVA (Table 2), the dose-normalized $C_{\max}$ values were not significantly different between various dose levels, except when comparing the 300- and 1,000-mg doses. However, the $C_{\max}$ difference between the 300- and

FIG. 2. Mean ($\pm$ standard deviation) plasma 935U83 concentration versus time curves following oral administration of single escalating doses under fasting conditions. ■, 100-mg dose; □, 300-mg dose; ◆, 600-mg dose; ○, 1,000-mg dose; ●, 1,500-mg dose.

FIG. 3. Mean ($\pm$ standard deviation) plasma concentration versus time curves of 935U83 and its glucuronide metabolite following single oral administration of 300 mg of 935U83 under fasting conditions or with a high-fat meal. ■, 935U83, with fasting; ●, 935U83, with food; □, 935U83 glucuronide, with fasting; ○, 935U83 glucuronide, with food. Concentrations of 935U83 glucuronide are expressed in 935U83 equivalents.

1,000-mg doses is minor and unlikely to be clinically significant. Values of $\ln(C_{\max})$ correlated linearly with $\ln(\text{dose})$ ($P < 0.0001$, $r^2 = 0.92$) with a slope of the regression line close to but less than 1.0 (mean, 0.92; 90% CI, 0.86 to 0.98). This indicates that $C_{\max}$ of 935U83 increases only slightly less than proportionally to the dose from 100 to 1,500 mg. When 300 mg of 935U83 was administered with a high-fat meal, the mean $C_{\max}$ value was reduced by approximately 50%. The fed-to-fasted $C_{\max}$ ratio has a mean value of 54% and a 90% CI of 41 to 71%.

The mean $t_{1/2}$ values of 935U83 were similar across all dose levels (range, 1.26 to 1.68 h), including the 300-mg dose administered with food (Table 2). The intersubject variability in

$t_{1/2}$ was relatively small, with individual values ranging from 0.96 to 2.15 h for all doses. Generally, the terminal linear portion of the semi-log plots of 935U83 at all dose levels were parallel within an individual volunteer.

Mean 935U83 $\text{AUC}_{0-\infty}$ values increased almost dose proportionally from 3.37 to 59.0 h $\cdot$ $\mu\text{g}/\text{ml}$ when the dose increased from 100 to 1,500 mg. Dose-normalized $\text{AUC}_{0-\infty}$ values were not significantly different between various dose levels except when comparing the 100- and 1,500-mg doses (Table 2). The dose proportionality in 935U83 $\text{AUC}_{0-\infty}$ was evident in the dose range of 300 to 1,500 mg. The 90% CI values for the linear regression line of $\ln(\text{AUC}_{0-\infty})$ versus $\ln(\text{dose})$ were 1.03 and 0.95 to 1.11, respectively. When 300 mg of 935U83 was administered with a high-fat meal, the mean $\text{AUC}_{0-\infty}$ value was essentially unaltered (11.1 versus 10.3 h $\cdot$ $\mu\text{g}/\text{ml}$). $\text{AUC}_{0-\infty}$ ratio, fed to fasted state, has a mean value of 91% and a 90% CI of 86 to 97%.

The mean CL/F of 935U83 ranged from 6.61 to 7.71 ml/min/kg and was not significantly different between dose levels, except when comparing the 100- and 1,500-mg doses (Table 2). The mean CL/F and individual CL/F values for a given subject were similar across the 100-to-1,500-mg dose range, showing little intrasubject variability.

935U83 glucuronide, the principal metabolite of 935U83, was detectable in the plasma of all subjects at all dose levels as early as 15 min and up to 12 h postdosing. 935U83 glucuronide concentrations (in 935U83 equivalents) were lower than those of the parent compound at almost all sampling times. The plasma concentration-time profiles of 935U83 glucuronide followed the general characteristics of those for the parent compound, except that the glucuronide profiles exhibited a lag time (Fig. 3). The effect of food on the plasma profiles of 935U83 glucuronide was similar to its effect on the parent drug, including reduced $C_{\max}$ and prolonged $T_{\max}$, without a change in $\text{AUC}_{0-\infty}$.

The $t_{1/2}$ s of mean 935U83 glucuronide were similar at all dose levels (mean, 1.2 to 1.4 h) and were similar to those of the parent compound. The ratio of the $\text{AUC}_{0-\infty}$ of 935U83 glucuronide to the $\text{AUC}_{0-\infty}$ of the parent compound was similar across all dose levels of 935U83 (mean, 21 to 27%).

The mean total percentage of the dose recovered in the 24-h urine and the percentages of the dose recovered as the parent compound and as the glucuronide metabolite were similar among all doses given with or without food, except at the 100-mg dose level (Table 3). In general, at least 60% of the 935U83 dose was absorbed with approximately equal percentages of the dose excreted as unchanged 935U83 ($\sim 30\%$) and as its glucuronide ($\sim 30\%$) in urine. CL_{RS} of both 935U83 and its glucuronide were similar among 935U83 dose levels from

TABLE 2. Statistical analysis of pharmacokinetic parameter estimates of 935U83 for escalating doses administered under fasting conditions^a

Dose (mg)	$t_{1/2}$ (h) ^b		CL/F (ml/min/kg)		Dose normalized ^c			
					$C_{\max}$ ($\mu\text{g}/\text{ml}$)		$\text{AUC}_{0-\infty}$ (hr $\cdot$ $\mu\text{g}/\text{ml}$)	
	LSM	95% CI	LSM	95% CI	LSM	95% CI	LSM	95% CI
100	1.39	1.28–1.52	7.49	7.07–7.93	2.27	1.97–2.61	3.29	3.11–3.49
300	1.32	1.22–1.44	6.83	6.42–7.26	2.55	2.19–2.97	3.63	3.41–3.87
600	1.25	1.15–1.36	6.93	6.52–7.38	2.00	1.72–2.33	3.57	3.36–3.81
1,000	1.39	1.28–1.53	6.84	6.43–7.28	1.85	1.59–2.16	3.63	3.41–3.86
1,500	1.63	1.47–1.82	6.48	6.09–6.90	1.99	1.71–2.32	3.83	3.59–4.07

^a Results determined based on ANOVA.

^b $t_{1/2}$ values [$t_{1/2} = \ln(2)/\lambda_z$] used to present statistical analysis results for λ_z .

^c Dose normalized to 100 mg.

TABLE 3. Mean urinary recovery data and renal clearances of 935U83 and 935U83 glucuronide in HIV-infected volunteers^a

Dose (mg), exptl condition	% Dose recovered as 935U83 (% CV)	% Dose recovered as 935U83 glucuronide (% CV)	Total urinary recovery [% dose (% CV)]	CL _{CR} [ml/min/kg (% CV)]	CL _R	
					935U83 [ml/min/kg (% CV)]	935U83 glucuronide [ml/min/kg (% CV)]
100, fasting	17.9 (56)	28.7 (51)	46.6 (42)	1.79 (15)	1.38 (59)	7.98 (42)
300, fasting	29.4 (30)	31.4 (35)	60.8 (19)	1.77 (17)	2.01 (33)	7.75 (28)
300, with food	26.1 (27)	29.9 (45)	56.0 (31)	1.81 (22)	1.97 (33)	8.31 (44)
600, fasting	34.8 (32)	29.8 (31)	64.6 (22)	1.78 (10)	2.38 (29)	8.63 (33)
1,000, fasting	36.3 (31)	28.9 (32)	65.2 (25)	1.81 (16)	2.50 (36)	8.20 (26)
1,500, fasting	34.5 (25)	26.8 (38)	61.3 (23)	1.82 (16)	2.22 (24)	8.11 (24)

^a $n = 12$ for the 100-mg dose; $n = 11$ for other doses. Values in parentheses are coefficients of variation (CV).

300 to 1,500 mg, with mean values of 2.22 and 8.20 ml/min/kg for 935U83 and its glucuronide, respectively. For comparison, the mean CL_{CR} estimated in individual volunteers was 1.42 ± 0.24 ml/min/kg (range, 1.18 to 1.86) at study entry and averaged 1.80 ml/min/kg (range, 1.23 to 2.81) throughout the treatment periods (Table 3). CL_R of 935U83 was significantly greater than the estimated CL_{CR} at doses of ≥ 600 mg ($P \leq 0.02$, paired t test). CL_R of 935U83 glucuronide was significantly greater than the estimated CL_{CR} at all doses ($P < 0.01$, paired t test).

DISCUSSION

The present study has characterized the plasma profiles of 935U83 and its principal metabolite, 935U83 glucuronide, following oral administration of single 100- to 1,500-mg doses in HIV-infected volunteers. 935U83 was rapidly and well absorbed following oral administration, which is consistent with previous observations in animals (5, 12). The mean C_{max} s of 935U83 were only slightly less than dose proportional in the dose range of 100 to 1,500 mg, although variable absorption characteristics of 935U83 were observed especially at higher doses. This variability may be due in part to the large number of tablets (up to eight) ingested at one time. 935U83 was rapidly eliminated from the plasma and its disposition followed linear kinetics in the dose range studies, as reflected by the similar $t_{1/2}$ and constant CL/F values among dose levels.

The intersubject variabilities in C_{max} , $AUC_{0-\infty}$, and $t_{1/2}$ of 935U83 were relatively small (coefficient of variation, $<21\%$), and the differences between the lowest and highest values for C_{max} , $AUC_{0-\infty}$, or $t_{1/2}$ among individuals across all dose levels were less than 2.5-fold. The low variability and consistent pharmacokinetic parameter estimates of 935U83 among different HIV-infected subjects are potential advantages of 935U83 as an oral antiretroviral agent, i.e., a narrow range of safe and effective doses may be defined in the targeted population. Plasma levels of 935U83 above the reported average in vitro IC₅₀ value for clinical HIV isolates (1.8 μ M or 0.48 μ g/ml) can be achieved following single oral administration of all doses studied (Fig. 2). However, the in vivo antiviral activity of 935U83 will depend on many factors (e.g., distribution into target cells, kinetics of intracellular phosphorylation, and triphosphate disposition) in addition to plasma concentrations.

Administration of 935U83 with food decreased the rate of 935U83 absorption but did not affect the extent of oral bioavailability of 935U83. The increased T_{max} (by about 1 h) and approximately 50% reduction in C_{max} by food intake have also been observed for other nucleoside antiretroviral agents such as zidovudine (13). The minor reduction in mean $AUC_{0-\infty}$ of 935U83 (from 11.1 to 10.3 h $\cdot$ μ g/ml) by food intake was not statistically significant and is unlikely to be clinically significant.

No specific dosing instructions for 935U83 with regard to food intake were incorporated in subsequent clinical trials of 935U83.

The plasma and urinary excretion profiles of 935U83 and 935U83 glucuronide indicate that the formation and elimination of 935U83 glucuronide follow linear kinetics (i.e., dose independent) in the 935U83 dose range of 100 to 1,500 mg. The similar $t_{1/2}$ s between 935U83 glucuronide and the parent 935U83 indicate that the disposition of 935U83 glucuronide is rate limited by its formation from 935U83. CL_Rs of 935U83 and 935U83 glucuronide were both greater than the estimated CL_{CR}, suggesting that the two compounds are secreted by renal tubules. 935U83, structurally similar to zidovudine, is less extensively metabolized via the glucuronidation pathway than zidovudine, i.e., the ratio of urinary recovery of the parent compound to that of the glucuronide was 1 to 1 for 935U83, while a ratio of roughly 1 to 5 was found for zidovudine (3).

Single oral doses of 935U83 up to 1,500 mg were well tolerated by HIV-infected subjects. No changes in hematologic parameters and no significant laboratory abnormalities were observed throughout the study. In subsequent multiple-dose clinical trials, 935U83 has been well tolerated at doses up to 1,300 mg given three times daily for 12 weeks or longer in HIV-infected patients (2, 6). This favorable safety profile of 935U83 is well supported by preclinical animal toxicology studies (5). In summary, this study confirms the desirable pharmacokinetic characteristics and the favorable safety profiles of single oral doses of 935U83 in HIV-infected individuals. Results of this study have supported the design of subsequent phase I/II clinical trials to evaluate the safety, antiviral activity, and pharmacokinetics of 935U83 as monotherapy and in combination therapy with other antiretroviral agents for the treatment of HIV infection.

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