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Pharmacokinetic Evaluations of Low- and High-Dose Zidovudine plus High-Dose Acyclovir in Patients with Symptomatic Human Immunodeficiency Virus Infection

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The pharmacokinetics of zidovudine were evaluated in 41 patients with Centers for Disease Control HIV class IVA infection. The patients were assigned escalating doses of zidovudine (300, 600, or 1,500 mg daily) and were randomized to receive either zidovudine alone or zidovudine with a high dose of acyclovir (4,800 mg per day). Single and multiple intravenous- and oral-dose pharmacokinetic studies were performed on days 1 and 7 and weeks 6 and 12 of therapy. Zidovudine concentrations were analyzed by high-pressure liquid chromatography. Pharmacokinetic parameters were estimated by noncompartmental methods. Zidovudine concentrations in serum declined in a biphasic manner, with half-lives ranging from 1 to 2 h, and were independent of acyclovir administration or length of zidovudine therapy. The median time of peak concentrations in serum following oral doses was 0.75 h (range, 0.25 to 3 h). Accumulation of zidovudine in serum was not observed, but the maximum concentration of drug in serum (C_{max}) and the area under the concentration-time curve increased proportionally with increased zidovudine doses. Mean day 7 oral C_{max} values were 0.20 ± 0.12, 0.55 ± 0.33, and 1.0 ± 0.5 μg/ml for 17 patients receiving total daily doses of, respectively, 300, 600, and 1,500 mg of zidovudine alone, whereas C_{max} values were, respectively, 0.27 ± 0.18, 0.43 ± 0.33, and 1.2 ± 0.80 μg/ml for 15 comparably treated recipients of zidovudine plus acyclovir (P was not significant). The median bioavailability of oral zidovudine was 67% (42 to 120%) and did not vary with dosage. Absolute and apparent total body clearances were similar among the patients given the various zidovudine doses regardless of whether there was concomitant acyclovir therapy. Drug-related toxicities were observed more frequently in the subjects who received high doses of zidovudine than they were in those who received median and low doses of zidovudine ($P = 0.03$). Overall, acyclovir did not influence the disposition of zidovudine over a wide range of zidovudine doses. No unusual toxicities could be attributed to the zidovudine and high-dose acyclovir combination during the 12-week observation period.

Zidovudine (formerly azidothymidine) the first licensed antiretroviral agent, is an inhibitor of human immunodeficiency virus (HIV) in vitro (17). Zidovudine therapy has been shown to be of benefit in patients with various stages of HIV disease, in that progression of HIV has been delayed in asymptomatic patients and development of opportunistic infections and mortality have been delayed in those with AIDS (5, 9, 22). The optimal means of enhancing the clinical efficacy and decreasing the toxicity of zidovudine have not been realized. Several strategies have been to decrease the dosage of zidovudine to reduce side effects and/or to add other compounds to enhance antiviral or clinical efficacy. Mitsuya and colleagues (16) reported that acyclovir concentrations exceeding 0.50 μg/ml potentiated the anti-HIV cytopathic effects of zidovudine (16) and that the 50% infective dose of HIV for zidovudine decreased with increasing acyclovir concentrations, such that ≤0.13 μg of zidovudine per ml and >8.0 μg of acyclovir per ml provided 100% protection from cytolysis. In early 1987, a dose ranging study to determine the antiviral effects and toxicities of various zidovudine doses alone or with concomitant acyclovir was initiated. The results of the antiviral and toxicity data from this trial have been reported recently (4). In this report we describe the pharmacokinetic aspects of that investigation.

MATERIALS AND METHODS

Subjects. Forty-one symptomatic HIV-infected homosexual males and one female with Centers for Disease Control HIV group IVA disease with a total CD4 count of 200 to 500 cells per mm^3 and who were either HIV p24 antigen positive or HIV plasma viremic were included in the AIDS Clinical Trials Group, protocol 010, of this study. Subjects had a mean age of 35.3 years (range, 23 to 64 years) and were within 20% of their ideal body weight. Subjects were excluded from the study if they were actively using drugs; if they received rifampin or anti-infectives within 14 days of entry; if there was evidence of moderate to severe gastrointestinal disturbances or renal, hepatic, and hematologic (other than lymphocytopenia) disease; or an AIDS-defining opportunistic infection or malignancy. All subjects signed a consent form approved by the Human Subjects Institutional Review Board of the University of Washington.

Study design and treatment assignment. This study was a nonblinded, randomized trial of six oral dosage regimens of either zidovudine and acyclovir or zidovudine alone. The treatment duration was 12 weeks. The subjects were assigned sequentially to one of three zidovudine dosages of

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300, 600, or 1,500 mg daily in six divided doses and were randomized to receive 4.8 g of acyclovir daily in six divided doses or zidovudine alone. The first 12 patients received 300 mg of zidovudine daily alone or with acyclovir. After completion of enrollment in the lowest-dose zidovudine group, the next 12 subjects were enrolled and randomized to receive the next highest dose of zidovudine alone or with acyclovir. Subjects were replaced if they did not complete the first 2 weeks of study.

Details of the clinical and virologic course of these subjects prior to and during the course of therapy have been published previously (4). In brief, clinical signs and symptoms of HIV infection improved significantly in subjects who received all three doses, including the lowest dosage, 300 mg daily. Weight gains and increases in CD4 counts were similar in all groups. Changes in HIV antigenemia and virus titers in plasma were similar in all three zidovudine treatment groups and were not affected by the use of acyclovir.

Pharmacokinetic studies. Subjects underwent pharmacokinetic studies at the Clinical Research Center at the University Hospital Medical Center. On day 1, zidovudine was administered alone as an intravenous (i.v.) infusion as 60% (average bioavailable dose) of the assigned oral dose (i.e., 30, 60, and 150 mg) and was infused over 30 min. Following an overnight washout period, subjects were given oral zidovudine (and acyclovir concomitantly if they were randomized to receive acyclovir) at their assigned doses. Prior to each kinetic study, individuals were instructed to abstain from solid food intake for at least 6 h prior to administration of their dose and did not eat for 2 h after the dose was administered. Subjects were then discharged and instructed to take their assigned treatment medication(s) for the next week.

During week 2, two additional pharmacokinetic studies were performed. Following the morning oral dose(s) of study drug(s) (ca. 8 a.m.), a zidovudine kinetic study was conducted over the 4-h dosage interval. The fourth 4-h kinetic study immediately followed; subjects were given their study medication(s) intravenously, zidovudine in the doses described above and acyclovir (if the subject was randomized to the acyclovir group) at 20% of the oral study dose (160 mg; average bioavailable dose) over 1 h. Subjects were discharged on the same day and instructed to continue taking their medications chronically for the study duration.

During weeks 6 and 12, subjects completed additional pharmacokinetic studies following oral zidovudine therapy. Zidovudine pharmacokinetics were determined over a 4-h dosage interval, as described above for study week 2.

Sample collection. (i) i.v. administration. Samples (5 ml) of venous blood were collected from an indwelling catheter that was placed in the arm opposite that in which drug was infused. The blood was placed in red-top separator tubes and was drawn at the described times following zidovudine administration: preadministration; exactly at the end of infusion; and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 h following infusion. During week 2, blood samples were obtained at the times indicated above, except that the blood specimens at 6.0 and 8.0 h were omitted.

(ii) Oral administration. Blood samples were collected on day 2 at the following times: preadministration and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, and 8.0 h following study doses. During weeks 2, 6, and 12, blood specimens were collected as described above, except the collections at 6.0 and 8.0 h were omitted.

Sample preparation and analysis. Following blood sample collection, the red-top tubes were stored upright in racks at room temperature for a maximum of 2 h. Serum was stored at −70°C until analysis. The zidovudine concentration in serum was determined by the method of Good et al. (12), with several modifications. Briefly, previously frozen serum samples were heat inactivated for 30 to 45 min at 56°C. Zidovudine was extracted on lipophilic type W columns by using a Du Pont Prep I automated sample processor (Du Pont Co., Wilmington, Del.); samples were placed on the columns, washed with phosphate-buffered saline, and eluted with methanol. The methanol was evaporated, reconstituted with 15% acetonitrile in water, and injected into the high-pressure liquid chromatography system. The column was a C_{18}-Resolve (5 μl; Waters Associates, Milford, Mass.). The mobile phase was 15% acetonitrile in 0.025 mol of potassium phosphate buffer (pH 2.20) per liter. The assay was capable of detecting as little as 0.04 μM zidovudine per liter. Interassay precision values (as percent coefficient of variation) for zidovudine were 5% (3.6 μM/liter), 5% (0.36 μM/liter), and 19% (0.08 μM/liter).

Pharmacokinetic analysis. Serum concentration data were analyzed by standard noncompartmental pharmacokinetic techniques. The terminal elimination phase was identified from inspection of zidovudine concentrations in serum, which were plotted semilogarithmically as concentration versus time since the last dose. Terminal elimination rate constants were initially estimated for each curve by using JANA, a curve-stripping computer program (7). PCNON LIN was subsequently used to verify the elimination rate constant from the initial estimate (20) by using only the terminal-phase concentration of drug in serum; the data set was treated as a bolus infusion and assumed a one-compartment model. A weighting scheme of reciprocal concentrations provided the estimate of best fit in most cases. The elimination half-life ($t_{1/2}$) was derived by dividing 0.693 by the terminal rate constant. The area under the serum concentration-versus-time curve (AUC) was determined by using the trapezoidal rule method (10). For single-dose studies, the AUC from the last point to infinity ($AUC_{t-\infty}$) was estimated by dividing the last concentration by the terminal rate constant.

Total body clearances (CLs) after i.v. doses were calculated by dividing the dose by the single- or multiple-dose AUC. The volume of distribution at steady state (V_{ss}) was obtained by using the standard statistical moments theory, with corrections for i.v. infusion time (10). For single-dose studies, the area under the moment curve (AUMC) was determined by the trapezoidal rule method extrapolated to infinity. Following steady-state studies, the AUMC was estimated by using reverse superposition, as reported by Bauer and Gibaldi (2).

Following administration of the oral dose, the maximum concentration (C_{max}) and the time to maximum concentration (T_{max}) in serum were obtained from inspection of the serum concentration-versus-time curves. The apparent CL following oral administration was calculated as bioavailability (F) times dose divided by AUC and was corrected for F when possible (10). An apparent V_{ss} was not calculated following oral administration, since the absorption rate constant could not be estimated.

Statistical analysis. To test for differences among treatment groups, a series of two-way analyses of variance were performed. For this model, two factors related to treatment were considered: the initial dose of zidovudine and the presence or absence of acyclovir. A separate analysis was performed for each of the outcome variables (i.e., C_{max}) and for each pharmacokinetic study. Differences in the treatment

TABLE 1. Characteristics of 41 patients with symptomatic HIV infection at the time of entry into the study

Treatment group[a]	Age (yr)[b]	Wt (kg)[b]	CD4 count (cells/mm^3)[c]	Karnofsky score[c,d]
1 (n = 8)	35.3 ± 10.3	74.5 ± 13.9	279 (200–484)	90 (80–90)
2 (n = 6)	33.3 ± 9.5	70.0 ± 10.0	321 (200–529)	90 (80–90)
3 (n = 7)	35.7 ± 12.8	66.4 ± 6.9	348 (215–413)	90 (80–90)
4 (n = 6)	33.3 ± 9.5	68.3 ± 6.7	428 (262–495)	90 (80–90)
5 (n = 7)	37.4 ± 11.4	76.3 ± 13.5	324 (380–562)	90 (80–90)
6 (n = 7)	35.5 ± 7.4	78.0 ± 5.6	333 (160–499)	85 (80–90)

[a] Treatment groups 1, 3, and 5 received oral zidovudine alone at 50, 100 and 250 mg every 4 h, respectively. Treatment groups 2, 4, and 6 received zidovudine at 50, 100, and 250 mg, respectively, plus acyclovir at 800 mg every 4 h.

[b] Values are means ± standard deviations.

[c] Values are medians (ranges).

[d] Score is based on a scale of 0 to 100, where 0 is death and 100 is fully physically and mentally functional.

means were examined to determine whether any difference was attributable to zidovudine, acyclovir, or some interaction between the two study medications. A P value of less than 0.05 was considered to be significantly different.

RESULTS

Of 41 subjects enrolled in the study, 38 subjects completed the first 2 weeks of the study. Fourteen subjects were not completely evaluable during study weeks 6 and 12 because of the development of AIDS (4), zidovudine toxicity (4), withdrawal from the protocol (2), and administrative discontinuation (4). Table 1 summarizes the characteristics of the subjects in each treatment group.

i.v. studies. Figure 1 shows the mean serum zidovudine concentration-time profiles for individuals who received 30, 60, or 150 mg of intravenous zidovudine on days 1 and 7 of the study either alone or with acyclovir. Zidovudine concentrations appeared to decline in a biphasic manner, with the elimination $t_{1/2}$ ranging from 1.3 to 1.8 h (Table 2). Elimination of zidovudine was found to be similar within and between treatment groups ($P > 0.05$) during study days 1 and 7. Maximum zidovudine concentrations at the end of infusion were 0.28 ± 0.13, 0.71 ± 0.38, and 2.4 ± 1.7 μg/ml on day 7 for subjects receiving 30, 60, or 150 mg of zidovudine i.v. plus acyclovir, respectively. In the treatment groups receiving 150 mg of zidovudine, peak zidovudine levels in serum were similar ($P > 0.05$) in those receiving zidovudine alone compared with those in subjects receiving concomitant acyclovir i.v.

CLs were available for most subjects in the i.v. studies and were found not to be significantly different between study days or treatment groups (Table 2). Likewise, V_{ss} estimates were similar between study doses. Subjects receiving 30 or 60 mg of zidovudine plus acyclovir i.v., had mean absolute V_{ss} values of 2.1 ± 0.7 and 1.8 ± 1.1 liters/kg,

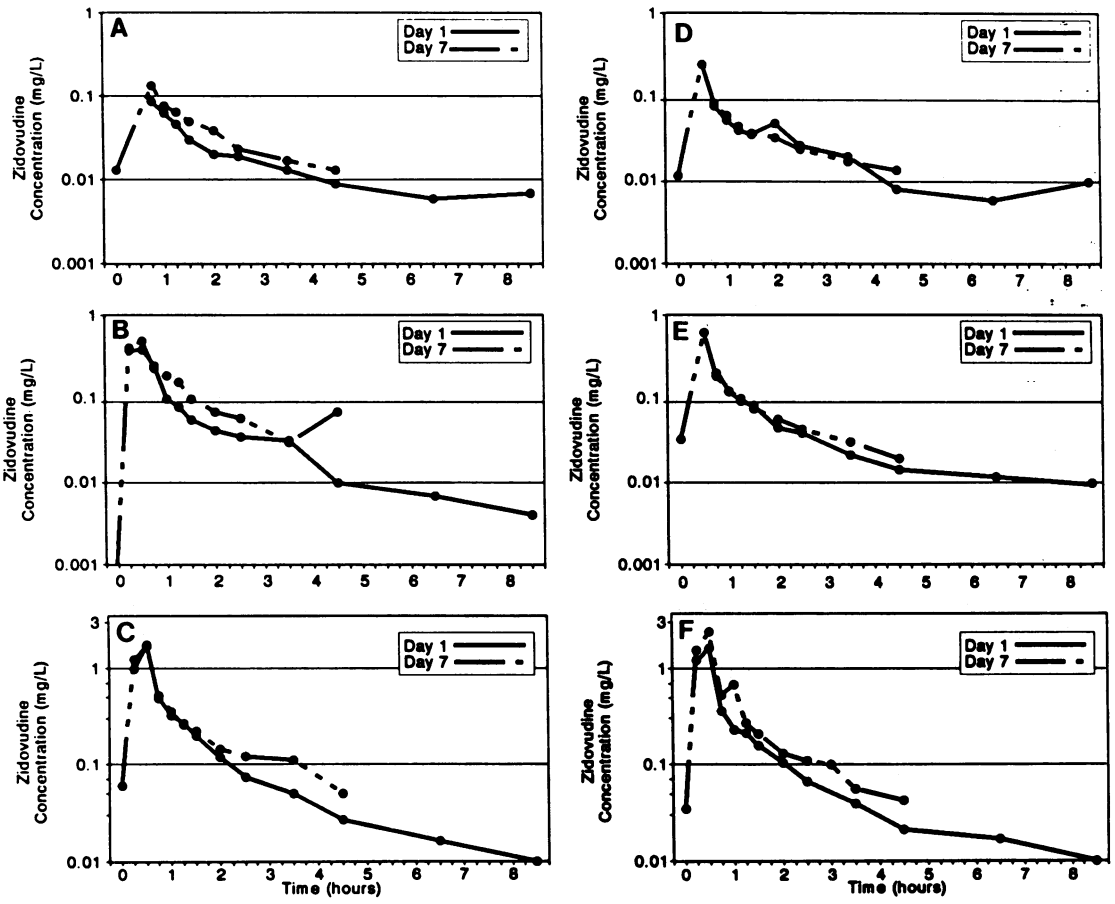

FIG. 1. Mean serum concentrations-versus-time profiles for subjects given zidovudine i.v. on days 1 and 7. (A to C) Subjects who received zidovudine alone; (D to F) recipients of zidovudine and acyclovir. (B) Following 60 mg of zidovudine; (C) following 150 mg of zidovudine.

TABLE 2. Pharmacokinetic parameters of zidovudine in symptomatic HIV-infected subjects receiving various i.v. or oral doses alone or in combination with high-dose acyclovir[a]

Treatment group[b]	No. of subjects	Dose (mg), route	Day	C_{max} (μg/ml)[c]	T_{max} (h)[c]	$t_{1/2}$ (h)[c]	AUC (mg/liter · hr)[c]	CL (liters/kg/h)[c,d]
1	5	30, i.v.	1	NA		1.5 ± 0.2	NA	NA
	6	50, p.o.	2	0.16 ± 0.05	1.00 ± 0.56	1.5 ± 0.3	0.26 ± 0.09	2.8 ± 0.5
	6	50, p.o.	7	0.20 ± 0.12	0.89 ± 0.66	1.4 ± 0.3	0.32 ± 0.14	2.4 ± 0.6
	7	30, i.v.	7	NA		1.3 ± 0.3	NA	NA
2	4	30, i.v.	1	NA		1.3 ± 0.5	NA	NA
	3	50, p.o.	2	0.23 ± 0.20	1.15 ± 1.07	1.3 ± 0.4	0.39 ± 0.17	2.1 ± 0.6
	5	50, p.o.	7	0.27 ± 0.18	0.60 ± 0.22	1.2 ± 0.3	0.33 ± 0.10	2.4 ± 0.6
	6	30, i.v.	7	0.28 ± 0.13		1.6 ± 0.3	0.27 ± 0.07	1.7 ± 0.4
3	3	60, i.v.	1	NA		1.3 ± 0.2	0.39 ± 0.17	3.0 ± 1.5
	6	100, p.o.	2	0.74 ± 0.55	0.64 ± 0.24	1.6 ± 0.4	0.74 ± 0.27	2.3 ± 0.6
	6	100, p.o.	7	0.55 ± 0.33	0.75 ± 0.42	1.1 ± 0.2	0.65 ± 0.16	2.5 ± 0.4
	4	60, i.v.	7	NA		1.5 ± 0.6	NA	NA
4	6	60, i.v.	1	NA		1.4 ± 0.2	NA	NA
	4	100, p.o.	2	0.74 ± 0.49	0.63 ± 0.47	1.2 ± 0.5	0.55 ± 0.16	2.8 ± 1.0
	5	100, p.o.	7	0.43 ± 0.33	0.63 ± 0.21	1.2 ± 0.3	0.71 ± 0.27	2.3 ± 0.9
	6	60, i.v.	7	0.71 ± 0.38		1.3 ± 0.2	0.57 ± 0.17	1.7 ± 0.5
5	5	150, i.v.	1	1.72 ± 0.74		1.7 ± 0.5	1.22 ± 0.39	1.8 ± 0.7
	5	250, p.o.	2	1.0 ± 0.50	0.82 ± 0.49	1.5 ± 0.2	1.33 ± 0.30	2.5 ± 0.4
	5	250, p.o.	7	1.0 ± 0.50	0.80 ± 0.41	1.1 ± 0.4	1.28 ± 0.26	2.6 ± 0.5
	4	150, i.v.	7	1.8 ± 0.50		1.4 ± 0.2	1.31 ± 0.38	1.5 ± 0.4
6	6	150, i.v.	1	1.8 ± 0.30		1.8 ± 0.6	1.31 ± 0.42	1.7 ± 0.5
	5	250, p.o.	2	1.2 ± 0.40	0.75 ± 0.38	1.7 ± 0.9	1.50 ± 0.46	2.5 ± 0.9
	5	250, p.o.	7	1.2 ± 0.80	0.83 ± 0.13	1.1 ± 0.2	1.43 ± 0.35	2.6 ± 0.8
	5	150, i.v.	7	2.4 ± 1.70		1.5 ± 0.3	1.86 ± 1.00	1.3 ± 0.5

[a] p.o., oral; C_{max}, maximum serum concentration; T_{max}, time of maximum serum concentration; $t_{1/2}$, elimination half-life; AUC, area under serum concentration-time curve; CL, total body clearance; NA, not available.
[b] Treatment groups 1, 3, and 5 received zidovudine alone; groups 2, 4, and 6 received zidovudine plus acyclovir at 800 mg every 4 h.
[c] Values are means ± standard deviations.
[d] Values following oral administration represent apparent estimates, that is, not corrected for *F*.

respectively ($P > 0.05$). Following administration of 150 mg of zidovudine, mean V_{ss} values were 1.8 ± 0.9 (day 1) and 1.4 ± 0.2 (day 7) liters/kg, whereas they were 1.5 ± 0.4 (day 1) and 1.3 ± 0.7 (day 7) liters/kg, respective-ly, for subjects concomitantly treated with 150 mg of zidovudine plus acyclovir ($P > 0.05$).

Oral studies. Figure 2 reveals the mean zidovudine concentration-time profiles for subjects who received 50, 100, or 250 mg of oral zidovudine, either alone or with acyclovir, and who underwent pharmacokinetic studies on days 2 and 7 and weeks 6 and 12. Maximum concentrations in serum occurred between 0.25 and 3 h, with a median T_{max} of 0.75 h for all treatment groups. Mean C_{max} values are given in Table 2. Mean C_{max} values and AUCs increased proportionally among subjects given the three zidovudine doses, regardless of concomitant acyclovir therapy, although there was much variability in C_{max} within and between subjects.

One individual who received 100 mg of zidovudine alone had a C_{max} on day 2 of 1.1 μg/ml, whereas on day 7 it was 0.2 μg/ml. Conversely, another subject who received 100 mg of zidovudine had C_{max} values of 0.54 and 1.1 μg/ml on days 2 and 7, respectively, which could not be attributed to accumulation. Similar inconsistencies in C_{max} values were observed in subjects concomitantly receiving acyclovir. C_{max} values following 250-mg oral doses were often much lower (about 70%) than i.v. peak values, even though i.v. doses were given at 60% of the oral dose. This difference may reflect a more variable rate of absorption following this high oral dose. The *F* value determined on days 2 and 7 in the group given 250 mg of zidovudine alone and the group given the combination ranged from 50 to 90% and 41 to 117%, respectively.

Apparent oral CLs were similar between the days of the study ($P > 0.05$) as well as between the six treatment groups ($P > 0.05$) (Table 2). The median CL following oral studies (corrected for *F*) was 1.8 liters/kg/h (range, 0.9 to 2.4 liters/kg/h).

Twenty-five patients completed the 6-week pharmacokinetic study, and 15 patients were available for follow-up at week 12. Pharmacokinetic parameters were not found to be clinically or statistically different at these time periods when they were compared with those in studies completed during the first 2 weeks of therapy. For example C_{max} values determined at week 6 were 0.19 ± 0.85, 0.61 ± 0.18, and 1.1 ± 0.60 μg/ml for those treated with, respectively, 300, 600, or 1,500 mg of oral zidovudine daily, whereas they were 0.26 ± 0.19, 0.62 ± 0.32, and 1.0 ± 1.0 μg/ml for acyclovir-treated subjects, respectively (*P* was not significant). CL/*F* values at week 6 for subjects treated with zidovudine (plus acyclovir) were 2.8 ± 0.7 (3.0 ± 0.9), 2.8 ± 0.5 (2.5 ± 1.0), and 2.6 ± 0.4 (2.8 ± 0.7) liters/kg/h for the escalating zidovudine doses, respectively.

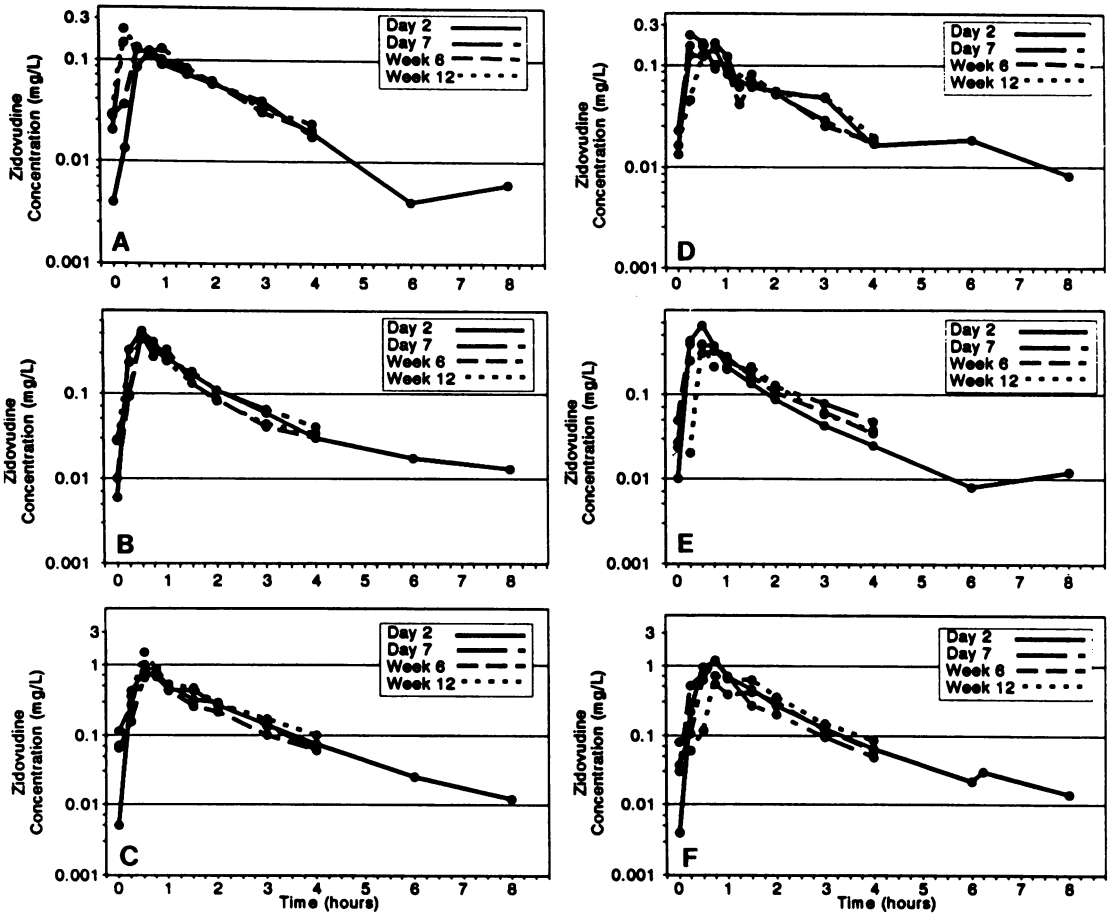

FIG. 2. Mean serum concentrations-versus-time profiles for subjects given zidovudine orally on days 2, 6, 7, and 12. (A to C) Subjects who received zidovudine alone; (D to F) recipients of zidovudine and acyclovir. (A) Following 50 mg of zidovudine; (B) following 100 mg of zidovudine; (C) following 250 mg of zidovudine.

DISCUSSION

In order to evaluate the pharmacokinetics of zidovudine in combination with high-dose acyclovir, we studied 41 patients with HIV infection during 12 weeks of chronic therapy. Following completion of six zidovudine pharmacokinetic studies, we observed that (i) high-dose acyclovir did not influence the disposition of zidovudine following administration of 300, 600, or 1,500 mg of oral zidovudine daily; (ii) peak oral zidovudine concentrations were highly variable within each dosage group; (iii) zidovudine levels in serum increased proportionally among the three doses studied; and (iv) no unusual toxicities were observed in patients who received the 12-week combination therapy compared with those who received zidovudine alone (4).

The accumulation of zidovudine in serum was not observed when single-dose data were compared with data from day 7 and weeks 6 and 12 among the zidovudine-alone or acyclovir combination treatment groups. This was expected, since the elimination of zidovudine is fairly rapid, with $t_{1/2}$s ranging from 1 to 2 h. Following 1 week of oral therapy, the mean peak concentrations of zidovudine in serum were 0.20 and 0.27, 0.55 and 0.43, and 1.0 and 1.2 μg/ml following administration of 50, 100, or 250 mg of zidovudine alone and with high-dose acyclovir, respectively. Although concentrations appeared to increase in a linear fashion, the C_{max} was highly variable within a given patient, with values differing as much as 150% over the course of this study. Inconsistencies in the rate of absorption or first-pass metabolism are the most likely explanations. AUCs, however, increased proportionally with rising zidovudine doses and with less variation, and were not different with concurrent acyclovir therapy.

Results of our study support what has been previously reported about the pharmacokinetics of zidovudine. The disposition of i.v. and oral zidovudine were initially described in patients with advanced HIV infection enrolled in phase I protocols (13). Zidovudine exhibited dose-independent pharmacokinetics until a dose of 10 mg/kg of body weight was administered i.v., at which point saturation of the major elimination pathway occurred (13). Elimination of zidovudine was primarily via hepatic glucuronidation with a short elimination $t_{1/2}$. Blum et al. (3) reported that levels in serum decayed biexponentially; however, Morse et al. (18) have noted that a third compartment is often apparent. In approximately 25% of our study participants who completed the 8-h intravenous study, we observed a second elimination phase, although we were unable to fully characterize it because there were few datum points. The elimination $t_{1/2}$s in our study were somewhat higher (1.5 h) than first reported by Klecker and coworkers (13) (1.0 h); this may be explained by the inclusion of third-compartment terminal datum points in our linear regression analysis. The significance of a third

tissue compartment is unclear. Apparent CL and absolute V_{ss} values for zidovudine were consistent within patients and among treatment groups in our study. While our CL values were in agreement with those reported by Klecker et al. (13) and Blum et al. (3), our V_{ss} values were usually 50% higher than their values. This finding is consistent with the findings described in another report (11) in which the volume of distribution was found to be higher than those found in earlier studies. Gitterman and colleagues (11) postulated that higher volumes of distribution may have resulted because their patients, as did ours, had an earlier stage of HIV disease. Other explanations include large variability in absorption and inaccuracy of sample collection times. The larger volumes of distribution reported probably reflect, in part, the lower levels of drug in the serum of some subjects, which may predict a lower risk of hematologic toxicity (11).

Acyclovir pharmacokinetics have been studied extensively following both oral and i.v. administration (6, 14, 19, 24). Because acyclovir has an elimination pathway different from that of zidovudine, it was not surprising that the pharmacokinetics of zidovudine were unaltered in the presence of acyclovir. A pharmacokinetic drug interaction was not apparent in our patient population. A report by Bach (1) suggested a possible drug interaction between zidovudine (1,200 mg/day) and acyclovir (15 mg/kg/day i.v.) therapy, in which a patient developed lethargy and fatigue with concurrent treatment. The patient's clinical status improved when oral acyclovir replaced parenteral therapy, but rechallenge with intravenous acyclovir produced overwhelming fatigue and deep sleep. Explanations for this case and other anecdotal reports of neurologic toxicity following concomitant zidovudine and acyclovir therapy cannot be based on higher than expected zidovudine levels in blood. Preliminary analyses of acyclovir concentrations in blood in our patients suggest, further, that zidovudine does not affect acyclovir concentrations in serum (21). Acyclovir alone has been reported to cause neurologic impairment, including seizures following high-dose i.v. therapy (23). As such, the experiences of Bach (1) and others with central nervous system toxicity following coadministration of zidovudine and acyclovir may be due solely to acyclovir or to coincident underlying HIV-associated neurologic problems.

Acyclovir is a well-tolerated nucleoside which independently lacks HIV activity, but it has been reported to be synergistic when it is combined with zidovudine in vitro (16). In a companion study to this pharmacokinetic study (4), we described that the antiviral and clinical effects of zidovudine at 300 mg/day appears to be similar to those of zidovudine at 600 or 1,500 mg daily. However, no discernible evidence of in vivo synergism between zidovudine and acyclovir was shown. Of potential clinical importance, however, is that we and others have not observed any additional toxicity when high doses of acyclovir were given concurrently with zidovudine (4, 15). Regardless of the lack of toxicity and pharmacokinetic interactions with this combination, we do not recommend that acyclovir be given routinely in combination with zidovudine for its effect against HIV. However, if patients have concurrent infection with a member of the herpesvirus group, the combination may be safely recommended. Additionally, one large study by a European/Australian collaborative group (8) has shown that for patients with AIDS who had a previous opportunistic infection, there was a significant improvement in survival for those who received the combination than in those who received zidovudine alone (85 versus 66%) for at least a 48-week period. The potential benefit of concomitant acyclovir and zidovudine on the morbidity and mortality of patients infected with HIV requires further study.

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