

## Pharmacokinetic Interaction of Megestrol Acetate with Zidovudine in Human Immunodeficiency Virus-Infected Patients

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This nonrandomized, two-period crossover study was performed to assess whether concomitant administration of megestrol acetate influences the steady-state pharmacokinetics of zidovudine and its inactive 5'-O-glucuronide metabolite. Twelve HIV-positive, asymptomatic male volunteers received a 100-mg oral capsule dose of zidovudine at least 30 min before meals five times a day at 0700, 1100, 1500, 1900, and 2300 h on study days 1 to 3 and a single 100-mg dose at 0700 h on day 4. On days 5 to 17, 800 mg of megestrol acetate, as a 40-mg/ml aqueous suspension, was administered orally immediately before the 0700 h dose of zidovudine. On days 5 to 16, zidovudine was also administered at 1100, 1500, 1900, and 2300 h. Serial blood samples were collected for 12 h after the single 100-mg dose of zidovudine on days 4 and 17; trough samples were also obtained just before the 0700 h dose on days 2 to 4 and 15 to 17. Levels of zidovudine and its glucuronide in plasma were assayed by a validated radioimmunoassay. Statistical analysis of trough plasma level data indicated that steady-state levels of zidovudine and its glucuronide in plasma had been attained when pharmacokinetic assessments were made on days 4 and 17. When megestrol acetate and zidovudine were coadministered for 13 days, differences of -14, -6.5, and -4.6% in mean zidovudine peak concentration and areas under the curve at 0 to 4 and 0 to 12 h, respectively, +22.5% in mean trough concentration, +2.6% in mean plasma half-life, and no change in median time to peak were observed compared to conditions when zidovudine was administered alone; for zidovudine 5'-O-glucuronide the respective differences were -9, -7.3, -4.4, +2.3, and +10% and no change. None of the differences were statistically significant ( $P > 0.05$ ). Concomitant therapy with megestrol acetate, at the dose employed to treat anorexia, cachexia, or an unexplained, significant weight loss in AIDS patients, did not alter the steady-state pharmacokinetics of zidovudine or its 5'-O-glucuronide metabolite.

Megestrol acetate (Megace) oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of AIDS (24, 29). Administration of a single 800-mg oral suspension dose daily results in increased food intake, body weight gain, and an improved sense of well-being. Consequently, megestrol acetate oral suspension may often be administered concomitantly with zidovudine (Retrovir) treatment in patients with AIDS. Zidovudine is absorbed rapidly from the gastrointestinal tract, and its systemic clearance is mainly by metabolism to the inactive 5'-O-glucuronide, which is excreted in the urine along with about 15% of the unchanged drug (20). Drugs affecting the pharmacokinetics of zidovudine interfere with its metabolic or renal clearance (3, 8, 30). However, no clear-cut recommendations for zidovudine dosage adjustment in patients receiving concomitant therapy with drugs known to result in pharmacokinetic drug interactions with zidovudine have been made, other than the recommendation for close monitoring for zidovudine toxicity with subsequent dosage adjustment as necessary.

The present study was designed to determine whether concomitant administration of megestrol acetate oral suspension, at a dose known to be effective in the treatment of significant weight loss secondary to anorexia and cachexia in AIDS patients, influences the steady-state pharmacokinetics of zidovudine and its 5'-O-glucuronide metabolite.

### MATERIALS AND METHODS

**Subjects.** Twelve HIV-positive (Western blot) asymptomatic male volunteers participated. All subjects were advised of the nature and risks of the study and gave written informed consent prior to enrollment. Their ages ranged from 24 to 49 years (mean, 36.4 years), heights ranged from 152.4 to 185.4 cm (mean, 175.2 cm), and weights ranged from 64.4 to 100.7 kg (mean, 80.6 kg). The subjects were in stable health as determined by prestudy medical histories and prestudy physical examinations and clinical laboratory test results as follows: hemoglobin,  $\geq 8.5$  g/dl; leukocytes,  $> 2,000/\mu\text{l}$ ; polymorphonuclear leukocytes,  $> 1,500/\mu\text{l}$ ; platelets,  $> 80,000/\mu\text{l}$ ; total bilirubin,  $< 1.5$  mg/dl; serum glutamic oxaloacetic and pyruvic transaminases and alkaline phosphatase more than twice the upper limit of normal; uric acid within normal limits; serum creatinine,  $< 2.0$  mg/dl; and a negative test for hepatitis surface antigens B and C. Exclusion criteria included regular use of medication within 1 week prior to the commencement of the study and during the study with the exception of zidovudine, vitamins, or intermittent use of aspirin, ibuprofen, or acetaminophen.

**Study design and dosing.** This was an open-label, nonrandomized oral pharmacokinetic study. Treatment for all subjects began with a 100-mg capsule dose of zidovudine five times a day at 0700, 1100, 1500, 1900, and 2300 h on study days 1 to 3 and a single 100-mg dose at 0700 h on day 4. On days 5 to 17, 800 mg of megestrol acetate, as a 40 mg/ml aqueous suspension, was administered immediately before the 0700 h dose of zidovudine. On days 5 to 16, zidovudine was also administered at 1100, 1500, 1900, and 2300 h. This multiple-dose schedule was employed to allow megestrol acetate, zidovudine, and zidovudine 5'-O-glucuronide to achieve steady-state levels in plasma before pharmacokinetic sampling was instituted. Capsules containing 100 mg of zidovudine and bottles containing 20 ml of megestrol acetate oral suspension, 40 mg/ml, were provided by Bristol-Myers Squibb Co. Each capsule dose was administered with about 200 ml of water. Subjects shook the bottle containing the 800-mg unit dose of megestrol acetate oral suspension and drank the contents of the bottle. The bottle was then filled with tap water (20 to 30 ml), capped, and shaken well, and the contents were swallowed. All drug doses were taken at least 30 min before meals, and on study days 4 and 17, when serial blood samples were drawn for pharmacokinetic determinations, the subjects fasted from 10 h before to 4 h after the single dose of zidovudine administered at 0700 h.

Clinical safety monitoring consisted of pre- and poststudy physical examinations and clinical laboratory tests, such as serum chemistry, hematology, and urinalysis. Monitoring of vital signs and queries for adverse reactions were also

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TABLE 1. Steady-state pharmacokinetic parameters for zidovudine and zidovudine 5'-O-glucuronide<sup>a</sup>

Analyte and treatments	$C_{\min}$ (ng/ml)	$C_{\max}$ (ng/ml)	$T_{\max}$ (h) <sup>b</sup>	$AUC_{0-4}$ (ng · h/ml)	$AUC_{0-12}$ (ng · h/ml)	$t_{1/2\beta}$ (h)
<b>Zidovudine</b>						
Zidovudine alone	30.6 ± 16.4	532.9 ± 176.5	0.63 (0.50–1.00)	778.5 ± 227.6	994.2 ± 302.9	4.53 ± 0.51 <sup>c</sup>
Zidovudine plus megestrol acetate	37.5 ± 21.5	458.2 ± 124.7	0.63 (0.25–2.00)	727.5 ± 202.9	948.9 ± 288.1	4.65 ± 1.24 <sup>c</sup>
<b>Zidovudine 5'-O-glucuronide</b>						
Zidovudine alone	106.4 ± 109.8	4,096 ± 1,413	0.88 (0.75–1.50)	5,156 ± 1,974	5,755 ± 2,243	2.43 ± 0.57
Zidovudine plus megestrol acetate	108.8 ± 105.5	3,724 ± 1,457	0.88 (0.50–3.00)	4,778 ± 1,349	5,502 ± 1,614	2.68 ± 1.08

<sup>a</sup> All values are means ± standard deviations for 12 subjects unless otherwise noted. The differences in values for all parameters between the treatments with zidovudine alone and with zidovudine plus megestrol acetate were statistically insignificant ( $P > 0.05$ ).

<sup>b</sup> Median (range).

<sup>c</sup> Mean ± standard deviation for 11 subjects; half-life was not calculable for one subject administered zidovudine alone.

conducted at various times during the course of the study. Subjects were discharged at the end of the study following final clinical and laboratory assessments.

**Blood sample collection and processing.** Venous blood samples (10 ml each) were collected by using Becton-Dickinson Vacutainers containing heparin as the anticoagulant. Serial blood samples were collected immediately prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h after the 0700 h dose of zidovudine on study days 4 and 17. Additional samples representing trough ( $C_{\min}$ ) levels were collected immediately before the 0700 h dose on study days 2 to 4 and 15 to 17 to evaluate the attainment of steady-state levels of zidovudine and its 5'-O-glucuronide metabolite in plasma. Immediately after collection, each blood sample was gently inverted a few times to ensure complete mixing with the anticoagulant and then centrifuged for 15 min at approximately  $1,000 \times g$  at about 5°C to separate the plasma. The plasma was then transferred to a screw-cap polypropylene tube, capped tightly, and stored frozen at or below -20°C until analysis.

**Assay of plasma samples.** The concentrations of zidovudine and its 5'-O-glucuronide metabolite were assayed in plasma samples by using a radioimmunoassay (RIA) kit (ZDV-TRAC<sup>125</sup>I RIA kit) available commercially from INCSTAR Corp., Stillwater, Minn., according to the methods outlined in INCSTAR technical bulletin 11688, revised September 1989. Megestrol acetate was demonstrated not to cross-react in the assay. A set of duplicate plasma standards containing zidovudine (6.4 to 625 ng/ml) or zidovudine 5'-O-glucuronide (26.6 to 2,600 ng/ml) were assayed in each assay run with appropriately spiked zidovudine or zidovudine-5'-O-glucuronide quality control (QC) samples and study samples in duplicate. The low standard concentration defined the lower limit of quantitation. Samples that assayed higher than the high standard were diluted into the range of the standard curve and reassayed. A portion of each plasma sample, standard, and QC were assayed for zidovudine by direct application of the commercial RIA assay for zidovudine, and another portion was assayed for zidovudine-5'-O-glucuronide. The glucuronide metabolite was converted to zidovudine with beta-glucuronidase by the assay procedure described in the RIA kit, with the exception that a 60- rather than a 30-min incubation time was employed. The concentration of zidovudine 5'-O-glucuronide was calculated by the following equation: [(converted assay concentration × 0.6024) - (zidovudine assay concentration)] × 1.66 = zidovudine-5'-O-glucuronide concentration. The factor of 1.66 is for the molecular weight difference between zidovudine and its glucuronide metabolite (1/1.66 = 0.6024). Predicted QC concentrations were within 14 and 15.5% of nominal for zidovudine and zidovudine-5'-O-glucuronide, respectively. The assay precision, measured as the coefficient of variation for QC samples, was about ±10% over the range of the zidovudine and zidovudine-5'-O-glucuronide standard curves.

**Pharmacokinetic analysis.** Plasma concentration-versus-time ( $C-t$ ) data for zidovudine and zidovudine-5'-O-glucuronide were analyzed by noncompartmental methods (9). The highest observed concentration in plasma for each analyte on days 4 and 17 and the corresponding sampling times are reported as  $C_{\max}$  and  $T_{\max}$ , respectively. Trough concentrations in plasma just prior to the 0700 h dose of zidovudine on days 2, 3, 4, 15, 16, and 17 are defined as  $C_{\min}$ . The terminal log-linear portion of the individual  $C-t$  curves was identified by the least-squares linear regression which yielded the smallest mean square error. Successive regressions of  $\ln C-t$  were performed starting with  $C_{\max}$  and ending with the last nonzero plasma concentration, using at least the last three nonzero concentrations. The elimination half-life ( $t_{1/2\beta}$ ) was calculated from the slope,  $\beta$ , of the terminal log-linear portion of the  $C-t$  curve by using the following relationship:  $t_{1/2\beta} = \ln 2/\beta$ . The area under the  $C-t$  curve (AUC) was calculated by the linear trapezoidal rule. The AUC from 0 to 4 h after the single 0700 h dose on days 4 and 17 was designated  $AUC_{0-4}$  and represents the AUC over the first 4-h dosing interval of the day at steady state. The AUC from 0 to 12 h after dosing on days 4 and 17 was designated  $AUC_{0-12}$ .

**Statistical methods.** Attainment of steady state for each analyte during each treatment, zidovudine alone (days 1 to 4) and zidovudine plus megestrol acetate (days 5 to 17), was evaluated by linear regression of the  $C_{\min}$  values obtained just before the 0700 h dose of zidovudine on study days 2 to 4 and 15 to 17. The

treatment means of the slope and intercept from each subject's regression were tested against a nominal value of zero by a one-sample  $t$  test. The steady-state (days 4 and 17) pharmacokinetic parameters  $C_{\max}$ , AUC,  $t_{1/2\beta}$ , and  $C_{\min}$  were analyzed by the paired Student  $t$  test. Steady-state  $T_{\max}$  values were compared by using Wilcoxon's signed rank procedure (13). All tests for significance were performed at the  $P = 0.05$  level.

## RESULTS

The mean steady-state  $C-t$  profiles for zidovudine and its 5'-O-glucuronide metabolite after the administration of zidovudine alone or concomitantly with megestrol acetate are shown in Fig. 1. An inspection of the profiles indicates that peak levels of both analytes in plasma were achieved within 1 h postdose regardless of treatment and that levels appeared somewhat lower for the first 2 h postdose when megestrol acetate and zidovudine were coadministered. However, mean levels in plasma from 2 to 12 h postdose were comparable for both treatments and declined in a parallel fashion. The semilog plot of the plasma zidovudine level data shows a distinct concavity between 3 and 6 h, and the decline in zidovudine 5'-O-glucuronide levels was also curvilinear. The terminal phase beyond 5 h was generally log-linear, suggesting an exponential decline in plasma levels. The mean pharmacokinetic parameter values (± standard deviation) calculated from the individual subjects'  $C-t$  data for zidovudine and its 5'-O-glucuronide are listed in Table 1. Statistical analyses of  $C_{\min}$  data, collected on study days 2 to 4 and 15 to 17, indicated that steady-state levels of zidovudine and its 5'-O-glucuronide in plasma had been achieved when pharmacokinetic assessments were made

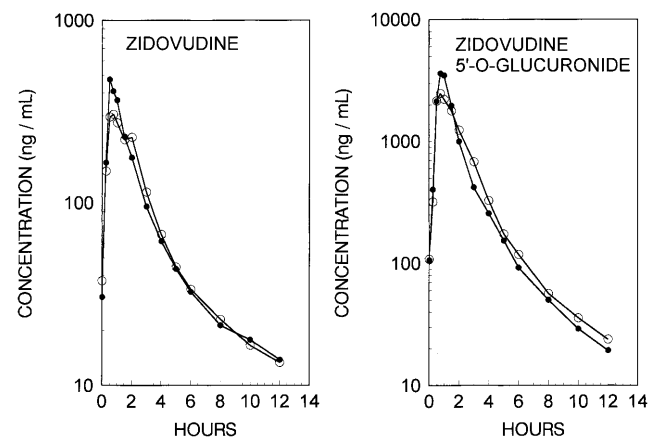


FIG. 1. Mean steady-state plasma concentration-time profiles for zidovudine and zidovudine 5'-O-glucuronide after administration of zidovudine alone (●) or concomitantly with megestrol acetate (○).

on day 4 (zidovudine alone) and day 17 (zidovudine plus megestrol acetate). When megestrol acetate and zidovudine were coadministered daily for 13 days, decreases of 14, 6.5, and 4.6% in mean zidovudine  $C_{\max}$ ,  $AUC_{0-4}$ , and  $AUC_{0-12}$ , respectively; a 22.5% increase in mean  $C_{\min}$ ; a 2.6% increase in  $t_{1/2\beta}$ ; and no change in median  $T_{\max}$  were observed compared to conditions when zidovudine was administered alone. For zidovudine 5'-O-glucuronide, the respective differences were -9, -7.3, -4.4, +2.3, and +10% and no change. In spite of the apparent differences in mean levels in plasma for the first 2 h postdose, the small differences in steady-state pharmacokinetic parameter values for zidovudine and its glucuronide metabolite between treatments were not statistically significant ( $P > 0.05$ ).

## DISCUSSION

The results of the present study reveal that when zidovudine and megestrol acetate oral suspension were coadministered, the steady-state pharmacokinetics of zidovudine and its 5'-O-glucuronide metabolite were not affected to any significant extent. Therefore, adjustment of the zidovudine dosage regimen is not necessary when megestrol acetate suspension is administered concomitantly to treat anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of AIDS. Since therapy with both drugs will usually extend over a prolonged period of time, it was important in the present study to evaluate the potential pharmacokinetic interaction between zidovudine and megestrol acetate after multiple doses. An accurate prediction of drug interaction under therapeutic conditions would not have been possible from a single-dose study. Although the present design does not exclude the possibility of period effects, it was chosen to complete the study as expeditiously as possible for these HIV-positive individuals who were already receiving zidovudine therapy prior to study entry.

Zidovudine is highly lipophilic and is rapidly distributed to deep tissue compartments (11, 14). Therefore, it seems reasonable to expect that the sensitive RIA employed in the present multiple-dose study would reveal the presence of a prolonged terminal elimination phase after chronic administration of zidovudine, a half-life that reflects disappearance from tissue compartments. A similarly prolonged mean terminal half-life was reported for zidovudine in another multiple-dose study (21). The lack of effect on steady-state AUC and terminal half-life values for zidovudine suggests that coadministration of megestrol acetate does not affect the tissue distribution of zidovudine.

Mechanisms of possible pharmacokinetic interactions between zidovudine and other drugs include effects on zidovudine metabolic and renal clearance (3, 8, 30). To date only a few interaction studies have demonstrated effects of other drugs on the pharmacokinetics of zidovudine or its inactive 5'-O-glucuronide metabolite. Probenecid (7, 15), valproic acid (17), fluconazole (27),  $\beta$  interferon (23), and atovaquone (16) have been shown to decrease the metabolic clearance of zidovudine by inhibiting glucuronidation, with a resultant increase in plasma zidovudine levels and half-life. Trimethoprim or trimethoprim-sulfamethoxazole have been shown to decrease the renal clearance of zidovudine and zidovudine 5'-O-glucuronide (5), likely through inhibition of the active tubular secretion of zidovudine. Rifampin, through induction of hepatic microsomal glucuronoltransferase, increases the metabolic clearance of zidovudine (4), with a resultant decrease in plasma zidovudine levels. The lack of a clinically relevant pharmacokinetic interaction has been demonstrated for several

drugs which may often be employed concomitantly with zidovudine, e.g., acetaminophen (2), didanosine (10, 19, 22, 26), zalcitabine (dideoxycytidine) (25), dipyridamole (12), foscarnet (1), naproxen (28), and oxazepam (18). The lack of effect of megestrol acetate on zidovudine pharmacokinetics observed in the present study seemed likely, as zidovudine is eliminated mainly by rapid hepatic metabolism to its 5'-O-glucuronide (20), which is subsequently excreted in the urine, while megestrol acetate is eliminated mainly by urinary excretion of the parent compound, likely via glomerular filtration with some passive tubular reabsorption, and to a lesser extent as sulfate- and glucuronide-conjugated products of oxidative metabolism (6).

In summary, results of the present study indicate that coadministration of megestrol acetate did not affect the steady-state pharmacokinetics of zidovudine or its 5'-O-glucuronide. This was shown by the absence of significant differences in steady-state  $C_{\min}$ ,  $C_{\max}$ ,  $T_{\max}$ , AUC, and  $t_{1/2\beta}$  values for zidovudine and zidovudine 5'-O-glucuronide when megestrol acetate suspension was coadministered with zidovudine compared to conditions with the administration of zidovudine alone. The lack of pharmacokinetic interaction is consistent with the aforementioned differences in the human disposition of zidovudine and megestrol acetate.

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