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Bioequivalence Assessment of Zidovudine (Retrovir) Syrup, Solution, and Capsule Formulations in Patients Infected with Human Immunodeficiency Virus

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The objectives of this open-labeled, multiple-dose, three-way-crossover trial were to evaluate the safety and tolerance of zidovudine (Retrovir) oral syrup and to assess the bioequivalence of this formulation relative to zidovudine solution and capsule formulations in human immunodeficiency virus-infected patients. Over the 7-day study, 12 adult male subjects received 12 administrations each of the capsule, solution, and syrup formulations every 4 h (six times daily) in a randomized sequence. Frequent blood samples were collected over the 4-h period after dose 12 was administered. Zidovudine concentrations in plasma were determined by a specific and sensitive radioimmunoassay. Results from statistical analyses indicated that all three formulations were bioequivalent with respect to systemic availability (area under the time-concentration curve) and that the syrup was also equivalent to the solution with respect to the maximum peak concentration in serum. The lower relative maximum peak concentration in serum (approximately 81%) and small delays in time to peak concentration (<30 min) of the capsule formulation as compared with the liquid formulations are thought to be due to the additional processes of disintegration and dissolution associated with capsule administration. All three preparations were well tolerated during the 7-day study.

Zidovudine (Retrovir) has been shown to be a potent in vitro inhibitor of human immunodeficiency virus replication (4). Phase I studies conducted in adult patients defined the absolute bioavailability of orally administered zidovudine (1, 3). Subsequent multicenter phase II studies demonstrated decreased mortality and reductions in the frequency and severity of opportunistic infections in patients with acquired immunodeficiency syndrome who had recovered from their first episode of *Pneumocystis carinii* pneumonia and/or who had decreased CD_4 lymphocyte counts (2). On the basis of these data, the Food and Drug Administration approved the marketing and distribution of Retrovir 100-mg capsules for select patient populations on 19 March 1987. However, this formulation does not satisfy the need to deliver flexible dose amounts in patients requiring modifications in therapy. Alternative preparations would also be desirable for patients with difficulties swallowing a solid dose form. In response to these needs, Retrovir (Burroughs Wellcome Co.) has been formulated in a syrup preparation.

It was the objective of this study to evaluate the bioequivalence of zidovudine syrup relative to solution and capsule formulations and to determine its safety and tolerability in human immunodeficiency virus-infected patients. This was performed by using an open-label, three-treatment (formulation), three-way-crossover study design.

MATERIALS AND METHODS

The protocol and informed consent were reviewed and approved by the Institutional Review Board at Duke University Medical Center. Twelve adult male patients, age 18 years or older, who were receiving and tolerating Retrovir capsules at a dosage of either 100 or 200 mg every 4 h for at least 1 week were recruited for this study. Patients were excluded from study participation if they presented with renal impairment (estimated creatinine clearance of $\leq$50 ml/min per 1.73 m^2 or serum creatinine of $\geq$2.0 mg/dl), liver dysfunction (alanine transaminase level greater than five times the upper limit of normal), Karnofsky status <60, known or anticipated requirement for concomitant therapy during the evaluation, a history of hypersensitivity to zidovudine, malabsorption syndrome or chronic diarrhea (four or more unformed [semisolid or liquid] stools per day for longer than a 4-week period accompanied by severe weight loss), the presence of an active, serious opportunistic infection, or the inability to give informed consent.

After obtaining informed consent, a medical history and physical exam were performed. Blood chemistries and hematologic parameters were determined prior to study entry. Each patient was randomly assigned to one of three sequences (capsule-solution-syrup, solution-syrup-capsule, or syrup-capsule-solution) by a computer, with four patients assigned to each sequence group.

Formulations used in this study were Retrovir strawberry-flavored syrup (10 mg/ml; batch 7X2705), Retrovir injection (20-mg/ml solution; batch 6B2744) administered orally, and Retrovir capsules (100 mg; batch 7T2735) supplied by Burroughs Wellcome Co.

Patients received 12 successive administrations of each formulation every 4 h at a dose consistent with their pre-study regimens (i.e., 100 or 200 mg). Each subject was instructed to fast from midnight before sampling until 4 h after the evaluation dose. Blood samples were obtained through an indwelling intravenous catheter at 0 (predose), 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, and 4 h after dose 12. Doses were administered orally in a total volume of 200 ml (formulation plus water). Vital signs were recorded on one occasion

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during sampling. Crossover was then performed to an alternate formulation at the same dose, with the above procedures repeated after dose 12 of each formulation.

Plasma samples were obtained from whole blood collected in a heparin-free Vacutainer (Becton Dickinson Vacutainer Systems) and frozen at −20°C. The assay of zidovudine concentrations in serum was performed using a sensitive and specific radioimmunoassay procedure described by Quinn et al. (J. Immunol., in press). The lower limit of detection of the assay was 0.1 μM (approximately 0.03 μg/ml).

Data on zidovudine concentrations in plasma were analyzed by noncompartmental pharmacokinetic methods. For each formulation, the maximum peak concentration in serum (C_{max}), time to peak concentration in serum (T_{max}), and area under the time-concentration curve (AUC) (estimated by trapezoidal approximation) were determined. Apparent total body clearance (CL/F) for each formulation and patient was calculated as the dose divided by AUC. Assuming that clearance did not change for a given patient across formulations, the bioavailability of one formulation relative to another was evaluated as the ratio of their AUCs. Elimination half-life ($t_{1/2}$) was estimated by log-linear least squares regression of the concentration-time data in the terminal phase.

Analysis of variance (ANOVA) using SAS software (5) was conducted to determine treatment differences in concentrations in plasma at the protocol sampling times and in the pharmacokinetic parameters AUC, C_{max}, T_{max}, CL/F, and $t_{1/2}$. Specific treatment comparisons made were syrup versus solution, syrup versus capsule, and capsule versus solution. Determinations were also made of the power of the ANOVA and of the 90% confidence intervals about the ratio of parameter means based on the two one-sided tests procedure (6).

RESULTS

Twelve adult males (one adult male with a history of intravenous drug abuse and eleven homosexual men) with a mean age of 32 years (range, 22 to 49 years) completed the study. All patients had normal renal and hepatic function as measured by serum creatinine and liver function tests performed prior to study entry, and all had a Karnofsky performance score ≥90 at the time of enrollment. During study participation, no concomitant medication was reported by patients with the exception of one dose of ibuprofen (200 mg) for headache in one patient. Compliance to medication administration schedules was excellent. No patient missed more than one dose per treatment period, and compliance was 100% in 8 of the 12 patients who completed the protocol.

The study population consisted of two subgroups receiving the drug in either 100- or 200-mg doses. Results from analysis (two-sided t test) of AUC and C_{max} at the two dose levels indicated dose proportionality for each of the formulations. Subsequent analyses, therefore, were conducted with data normalized to doses of 200 mg. Mean normalized steady-state zidovudine concentrations in plasma are illustrated in Fig. 1. The pharmacokinetic parameter estimates for each formulation are summarized in Table 1.

The mean steady-state AUCs were identical for the syrup and solution and about 10% greater for the capsule formulation. The mean relative bioavailability estimates, as determined from individual patient AUC ratios, were 1.00 ± 0.12 (syrup to solution), 0.95 ± 0.21 (syrup to capsule), and 1.04 ± 0.22 (capsule to solution). The mean C_{max} for the capsule

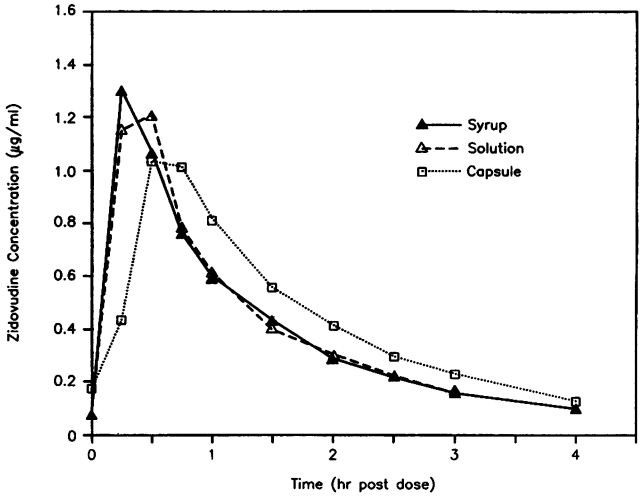

FIG. 1. Mean steady-state zidovudine concentrations normalized to a 200-mg dose.

was about 81% of that for the liquid formulations, and the mean T_{max} for the capsule averaged about 20 min greater than that for the syrup and solution formulations. Apparent CL/F and $t_{1/2}$ were constant for each of the formulations.

Results from statistical analyses comparing pharmacokinetic parameter estimates for each formulation are summarized in Table 2. By the ANOVA approach, no differences could be detected in AUC, C_{max}, CL/F, or $t_{1/2}$ at the 5% level among the three formulations. Overall, the only significant difference in pharmacokinetic parameters at the $P \leq 0.05$ level was the time to peak concentration, with powers of the analysis to detect a 20% difference in the overall normalized parameter means of 0.80, 0.31, and 0.25 for AUC, C_{max}, and T_{max}, respectively. The low power for C_{max} is probably attributable to patient variability in addition to the small sample size. The low power for T_{max} should also include differences owing to formulation. The mean T_{max} values for the syrup and solution formulations were less than that for the capsule ($P \leq 0.001$). No significant differences were detected between concentrations at any time point after the administration of the syrup and solution formulations. However, the concentration for the capsule formulation was significantly lower than those for both the syrup and solution at the 0.25-h sampling time ($P \leq 0.01$), and concentrations from capsule dosing were significantly greater than those from the liquid formulations at all sampling times between 0.75 and 3.0 h, inclusively ($P \leq 0.02$). Results from analyses by the two one-sided tests procedure indicated bioequivalence with respect to AUC, CL/F, and $t_{1/2}$ for all three formulations, in that the 90% confidence intervals about the ratio of formulation means all fell within the standard equivalence interval of 0.8 to 1.2. By the same test, there was no difference in C_{max} resulting from syrup and solution dosing, but C_{max} from capsule administration was significantly lower than that from dosing with either of the liquid formulations.

In general, all three zidovudine formulations were well tolerated. All vital signs were normal at entry and remained stable throughout the study period. Four patients (33%) reported clinical adverse experiences associated with zidovudine dosing. The most frequently reported adverse experience was nausea. Three patients (25%) reported nausea during dosing with solution, with one continuing to complain of nausea through day 2 of syrup administration. Two patients (16.7%) reported headaches during administra-

TABLE 1. Mean (± standard deviation) noncompartmental pharmacokinetic parameter estimates (normalized to a 200-mg dose)

Retrovir formulation	AUC (μg · h/ml)	C_{max} (μg/ml)	T_{max} (h)	CL/F (ml/min)	$t_{1/2}$ (h)
Syrup	1.65 ± 0.76	1.55 ± 0.82	0.46 ± 0.28	2,321 ± 784	1.03 ± 0.22
Solution	1.65 ± 0.71	1.50 ± 0.56	0.38 ± 0.14	2,297 ± 736	1.12 ± 0.28
Capsule	1.81 ± 0.90	1.23 ± 0.50	0.76 ± 0.30	2,188 ± 854	1.04 ± 0.26

tion of solution. One patient (8.3%) experienced flatulence during administration of all three formulations.

DISCUSSION

The pharmacokinetics and bioavailability of zidovudine following single and multiple doses of zidovudine given orally and intravenously have recently been reported by Blum et al. (1). Overall bioavailability was determined to be approximately 65% for the solution and capsule formulations. Based on urinary recovery of the parent compound and known metabolite, the incomplete bioavailability was attributed to first-pass metabolism rather than incomplete absorption.

Data from the present study suggest that zidovudine is rapidly absorbed. As anticipated, zidovudine from the solution and syrup formulations was more rapidly absorbed than from the capsule formulation. The differences in concentrations in plasma at various sampling times and in the parameters T_{max} and C_{max} are presumably due to the greater rate of drug absorption associated with the liquid formulations when compared with the capsule as a result of the additional disintegration and dissolution requirements of the solid dose form prior to absorption. No differences were observed in AUC, the primary measure of drug exposure, among the three formulations.

TABLE 2. Summary of statistical results on pharmacokinetic parameters

Parameter	ANOVA *P* value	Power of ANOVA	90% Confidence interval
Syrup vs solution			
AUC	0.994	0.80	0.91–1.09
C_{max}	0.797	0.31	0.87–1.20
T_{max}	0.352	0.25	0.92–1.47
CL/F	0.859	0.91	0.93–1.09
$t_{1/2}$	0.184	0.82	0.83–1.00
Syrup vs capsule			
AUC	0.177	0.80	0.83–1.00
C_{max}	0.098	0.31	1.06–1.46
T_{max}	0.001	0.25	0.47–0.74
CL/F	0.327	0.91	0.98–1.14
$t_{1/2}$	0.851	0.82	0.90–1.08
Capsule vs solution			
AUC	0.175	0.80	1.01–1.19
C_{max}	0.155	0.31	0.65–0.98
T_{max}	<0.001	0.25	1.71–2.25
CL/F	0.419	0.91	0.88–1.03
$t_{1/2}$	0.250	0.82	0.83–1.01

On the basis of the study data and the statistical analyses used, we conclude that zidovudine syrup was bioequivalent to both solution and capsule formulations with respect to AUC and to the solution formulation with respect to C_{max}. Although the capsule formulation is generally more slowly absorbed than the syrup and solution formulations, the difference (<30 min) in T_{max} is not expected to have any clinical consequences. In general, all preparations were well tolerated over the 7-day study period.

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