The Effect of Food on Pharmacokinetics of Zalcitabine in HIV-Positive Patients

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Purpose. The purpose of this study was to determine the effect of food on the pharmacokinetics of zalcitabine in HIV-positive patients.

Methods. Twenty patients received single oral 1.5 mg doses of zalcitabine with and without a standard breakfast in an open-label, randomized crossover study with at least a one week washout period between treatments. Serial blood and urine samples were collected over 24 hours and assayed for zalcitabine by a modified GC/MS method.

Results. Administration with food delayed and prolonged absorption resulting in a decrease of approximately 39% in maximal plasma concentrations compared to dosing under fasting conditions. Comparison of plasma AUC values indicated a small (14%) reduction in bioavailability when given with food. Approximately 59% and 45% of the dose were excreted unchanged in the urine under fasting and fed conditions, respectively.

Conclusions. The results of this study show that the administration of zalcitabine with food results in a mild reduction in bioavailability. Although these changes are not expected to be of clinical importance, further studies must be conducted for confirmation.

KEY WORDS: pharmacokinetics; food; interaction; zalcitabine; HIV infection.

INTRODUCTION

Zalcitabine (formerly ddC or dideoxycytidine) is one of several pyrimidine nucleoside analogs (others are zidovudine and didanosine) that has been shown to inhibit HIV replication "in vitro" and "in vivo". It has been approved for the treatment of HIV infection in adults with advanced HIV disease who either are intolerant to zidovudine (ZDV, Retrovir®) or who have disease progression while receiving zidovudine. It is also approved for use in combination with zidovudine for the treatment of selected patients with advanced HIV disease (CD4 cell count $\leq$ 300 cell/mm^3). Pharmacokinetic studies in adult HIV-positive patients or patients with AIDS or ARC (AIDS-related complex) show that zalcitabine is rapidly and extensively absorbed after oral administration, and subsequently eliminated with a half-life ranging from 1 to 3 hours. Renal excretion of unchanged drug is the primary route of elimination, accounting for 60 to 70% of an oral dose within 24 hours after dosing. Renal clearance of zalcitabine exceeds glomerular filtration rate, suggesting that tubular secretion contributes to the renal elimination of the drug. (1–3)

The presence of food has been shown to alter the absorption of many drugs (4,5). Previous studies with other antiretroviral nucleoside analogs show that food delayed absorption and reduced bioavailability of zidovudine (6,7) and didanosine (8). Zalcitabine is typically administered three times daily and, because of this regimen, doses are often taken in close temporal relationship with meals. Presented herein are the results of a study which was designed to evaluate the influence of food on the absorption and bioavailability of zalcitabine.

(The results of this study were presented in part at the Seventh Annual AAPS Meeting and Exposition on November 15–19, 1992 in San Antonio, Texas.)

MATERIALS AND METHODS

Patient Selection

Eighteen male and two non-pregnant female HIV-positive patients completed the study. They were all ambulatory ranging in age from 29–47 years and weighing 56–108 kg. The patients were either asymptomatic or had symptomatic AIDS or ARC. At the time of entry into the study, each patient was free of opportunistic infections and demonstrated normal renal and hepatic function. In addition, a hemoglobin of a least 9.5 gm/ml, absolute neutrophil count $\geq$ 1000 cells/mm^3, a platelet count $\geq$ 100,000 platelets/mm^3 and an estimated creatinine clearance $\geq$ 75 ml/min were required. Patients who received drugs with potential to cause peripheral neuropathy were excluded as were active drug or alcohol abusers. Patients with a fever >38.5°C or with significant cardiac and gastrointestinal disease were ineligible for the study. Patients with intolerance to lactose or nucleoside analogs were also excluded. The protocol was reviewed and approved by the Investigational Review Board of the Newark Beth Israel Medical Center and each patient gave written informed consent to participate in the study.

Experimental

Within 1 month prior to the start of the study, a medical history, physical examination and laboratory tests were performed on each patient. The laboratory tests consisted of blood chemistry, hematology and urinalysis. Alcohol was excluded for 72 hours prior to each dosing and until being discharged from the unit. Women were tested for pregnancy to assure negative status. The patients were confined to the study unit approximately 12 hours prior to the start of each study interval. A light snack was served 10 hours prior to dosing after which an absolute fast except for water was maintained. Water was allowed *ad libitum* throughout the study. In the morning, patients received a single oral dose of 1.5 mg zalcitabine as 4 × 0.375 mg tablets with or without a standard breakfast according to a randomized schedule. (Note: This study was conducted as a four-way crossover design assessing uncoated and film-coated tablets, under fed and fasting conditions; however, only the data regarding the

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market film-coated formulation are reported.) The tablets were ingested halfway through a standard breakfast with 240 ml water. The standard breakfast consisted of 2 eggs, fried in 1 tsp. butter/margarine, 2 strips bacon, 2 slices white toast with 2 tsp. butter/margarine, 8 oz. whole milk and 4 oz. hash brown (9).

Blood samples were drawn into heparinized Vacutainer tubes prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 10 hours post dose and centrifuged immediately. The total volume of urine voided was collected for two hours prior to each study treatment and at 0–12 and 12–24 hour intervals post-dose. Plasma and urine samples were stored at −70°C until analysis. Samples were handled in accordance with CDC criteria (10).

Patients remained upright (seated or ambulatory) for at least 4 hours after dosing. Following the standard breakfast, the fast was resumed until the 4 hour blood samples were collected after which a standard lunch was served. No food was allowed between lunch and dinner. Dinner was served 10 hours after dosing; thereafter, food was allowed *ad libitum*. Patients remained in the study unit until the 24 hour urine collection was completed. A washout period of at least one week separated the treatments.

Sample Analysis

Plasma and urine concentrations were determined by a modified gas chromatographic-mass spectrometric (GC-MS) method (11). The assay for zalcitabine in plasma showed overall inter- and intra-assay precisions of 4.1% and 8.7%, respectively, and a lower limit of quantification of 2.0 ng/ml using 1.0 ml of plasma. The assay for zalcitabine in urine showed overall inter- and intra-assay precisions of 2.4% and 5.2%, respectively, and a lower limit of quantification of 29.94 ng/ml using 0.2 ml of urine.

Data Analysis

Pharmacokinetic parameters were calculated by model-independent methods as follows. Maximum plasma concentration (C_{max}) and the time of maximum plasma concentration (t_{max}) were read directly from the plasma concentration-time data. The area under the plasma concentration-time curve from time zero to infinity (AUC) was determined by conventional linear trapezoidal summation and extrapolation methods. The elimination rate constant (β) was estimated by linear least-squares regression analysis on the terminal log-linear portion of the plasma concentration-time curve. The elimination half-life ($t_{1/2}$) was calculated as ln 2/β. The concentration of drug in urine and the total urine output were used to calculate the urinary excretion of zalcitabine during each collection interval and the overall excretion of drug during the entire collection period (Xu). The fraction of dose excreted unchanged in the urine (f_e) during the entire collection period was calculated as Xu/Dose. The renal clearance (Cl_r) was determined as the total urinary recovery (Xu) divided by AUC. The standard analysis of variance for cross-over designs including a test for a first-order carryover effect and the Two One-Sided Tests procedure were used to analyze the bioavailability variables (12,13). The 90% confidence interval (CI) for the ratio of fed to fasted means are provided. Bioequivalency of the formulation given under fed and fasted conditions was established when the 90% CI fell within the interval 0.80 to 1.20.

RESULTS

The most frequent clinical adverse experiences reported were headache and dizziness that ranged from mild to severe in intensity. In most cases, these adverse experiences were judged by the investigator to be remotely or possibly related to the drug.

A summary of the pharmacokinetic parameters [Mean (%CV) and Range] is presented in Table I. The mean plasma concentration-time curves for the fasted and fed state are illustrated in Figure 1.

Maximum plasma concentrations averaged 0.8 hr when drug was given under fasting conditions and 1.6 hr when given with a standard breakfast. This prolonged absorption resulted in a reduction of mean C_{max} by approximately 39% ($p < 0.01$ by ANOVA). Mean AUC decreased by 14% in the presence of food ($p < 0.01$ by ANOVA). The elimination half-life remained unchanged in the presence of food. Based on the Two One-Sided Tests Procedure, there was insufficient evidence to establish bioequivalence between zalcitabine given with food and under fasting conditions (Table I). Zalcitabine was primarily excreted as unchanged drug in the urine over the 24 hour collection period (Table I). Approximately 59% and 45% of the dose were excreted renally under fasting and fed conditions, respectively. These results are consistent with those in plasma which showed that adminis-

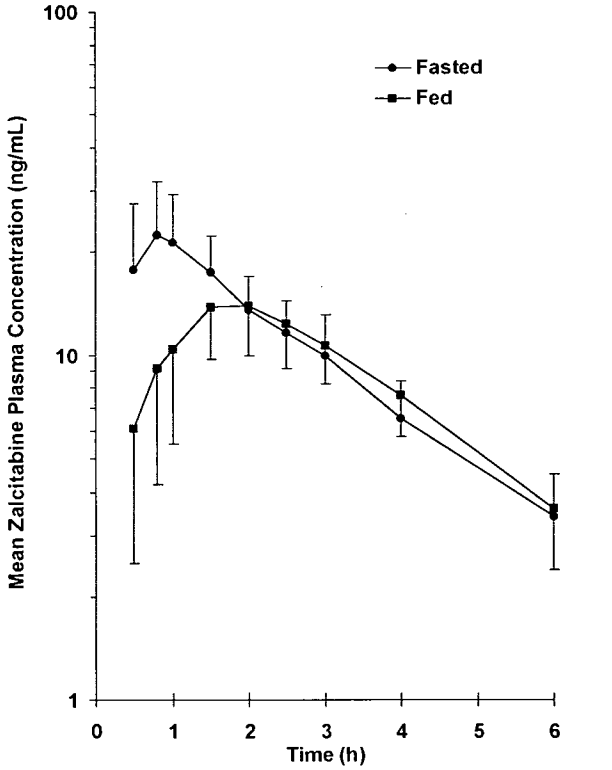

Fig. 1. Mean (±SD) plasma concentration-time profiles of zalcitabine following single oral administration of 1.5 mg in a fasted and fed state.

Table I. Summary of Zalcitabine Pharmacokinetic Parameters [Mean (%CV) and Range, N = 20]

Parameters	Fasted	Fed	90% CI for fed/fasted means
C_{max} (ng/ml)	25.2 (35) [11.6–38.6]	15.5 (24) [9.1–23.7]	0.52–0.70
t_{max} (hr)	0.8 (33) [0.5–1.5]	1.6 (34) [0.8–3.0]	1.83–2.40
AUC (ng · hr/ml)	72 (28) [43–119]	62 (23) [42–91]	0.79–0.93
β (hr^{-1})	0.366 (17) [0.247–0.445]	0.363 (18) [0.224–0.474]	−0.027–0.022[a]
$t_{1/2}$[b] (hr)	1.9 [1.6–2.8]	1.9 [1.5–3.1]	—
Cl_r (ml/min)	213 (41) [32–348]	195 (53) [14–437]	—
f_e (0–24 hr)	0.59 (36) [0.09–0.99]	0.45 (47) [0.03–0.79]	—

[a] 90% CI for fed mean minus fasted mean (CI = Confidence interval).
[b] Harmonic mean.

tration of zalcitabine with food results in a mild decrease in bioavailability.

DISCUSSION

During treatment of AIDS, zalcitabine is used chronically and it is expected that many doses will be taken with meals or in close temporal relationship to food. For this reason, it is important to understand if the presence of food alters its absorption. The present study was designed to evaluate the bioavailability of zalcitabine in the presence and absence of food.

In the absence of food, zalcitabine was rapidly absorbed, resulting in variable but maximal plasma concentrations within 1 hour in all but one patient. Subsequently, plasma concentrations declined rapidly with a mean elimination half-life of approximately 2 hours. Renal excretion of unchanged drug was the primary route of elimination, accounting for approximately 60% of the dose within 24 hours after dosing. These results are in general agreement with previous studies in which the drug was administered under fasting conditions (1–3).

When zalcitabine was given with a standard breakfast, absorption was delayed, resulting in a two-fold increase in t_{max}. Maximal levels were achieved within one hour postdose in only 5 of 20 patients but within two hours in all but two patients. The mean maximal plasma concentration was 39% lower, probably due to delayed and prolonged absorption over a longer time interval when the drug was given with food. In addition, there was a 14% reduction in mean AUC, indicating a mild but statistically significant (ANOVA) reduction in bioavailability when zalcitabine is administered with food. Renal clearance values observed in this study (213 and 195 ml/min for fasting and fed, respectively) exceed glomerular filtration rate, indicating that tubular secretion of zalcitabine contributes to its elimination by the kidney. Recovery of unchanged drug in the urine was consistent with results in plasma.

Studies have been previously conducted to evaluate the effect of food on the pharmacokinetic profiles of two other nucleoside analogs, zidovudine (6,7) and didanosine (8). Ruhnke et al. (6) showed that coadministration of single 100 mg and 250 mg oral doses of zidovudine with a standard breakfast resulted in a 37% and 73% reduction in mean C_{max}, respectively, and a nearly two-fold increase in half-life. Mean AUC was reduced by 33% and 14%, respectively. These results were similar to an earlier study conducted in a small number of HIV-positive patients by Unadkat et al. (7) in which zidovudine was administered with and without a high-fat meal. Shyu et al. (8) reported a 50% decrease in C_{max}, AUC and f_e following single oral administration of a 375 mg dose of didanosine with food. Because the results of these studies suggested that drug administration in the presence of food resulted in substantial delays in absorption and/or reductions in bioavailability, the authors recommended that zidovudine and didanosine are administered on an empty stomach. The bioavailability of zalcitabine observed in the present study was modestly reduced by 14%. Although this reduction is not expected to be of clinical importance, further studies are necessary for confirmation since a clear relationship between plasma concentrations of anti-retroviral agents and efficacy has not been established.

We note that the patients who participated in this study, although positive for the HIV virus, were generally asymptomatic or mildly symptomatic for AIDS. As such, gastrointestinal function in most of these patients was within normal limits. It is not known if similar results would be seen in patients with diarrhea or malabsorption associated with more serious AIDS. Two patients in the present study were being treated for diarrhea. Neither of these patients showed clear reductions in bioavailability in either the fasting or fed state compared to other patients in the study.

In conclusion, administration of zalcitabine with food results in delayed absorption and a mild reduction in bioavailability. Although the magnitude of these changes is not expected to be of clinical importance or to necessitate modifications in dosing when the drug is given with food, further studies must be conducted for confirmation.

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