
Absence of Food Effect on the Pharmacokinetics of Telbivudine Following Oral Administration in Healthy Subjects

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The influence of food on the pharmacokinetics of telbivudine, a candidate antiviral agent against hepatitis B virus (HBV), was investigated in healthy adult subjects following a 600-mg oral dose administered with and without a high-fat/high-calorie meal. Telbivudine was well tolerated under fasting and fed conditions. Oral absorption of telbivudine as measured by maximum plasma concentration (C_{\max}), time to reach C_{\max} (T_{\max}), and area under the plasma concentration-time curve (AUC_{0-t} and $AUC_{0-\infty}$) was not altered by food intake immediately before oral dosing. Values of C_{\max} , T_{\max} , and

AUC were comparable when telbivudine was administered under fed and fasting conditions. Results from this study indicated that the absorption of telbivudine was not affected by a high-fat/high-calorie meal; telbivudine can therefore be administered orally with no regard to the timing of meals.

Keywords: Telbivudine; hepatitis B; antiviral; pharmacokinetics; food effect

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Telbivudine (β -L-2'-deoxythymidine) is an L-configured nucleoside analogue with potent and specific antiviral activity against hepadnaviruses including hepatitis B virus (HBV), woodchuck hepatitis B virus (WHBV), and duck hepatitis virus and no appreciable activity against HIV or other viruses.¹ The in vitro median effective concentration (EC_{50}) of telbivudine in reducing extracellular DNA in the HBV-expressing hepatoma cell line 2.2.15 was 0.19 μ M. In woodchucks chronically infected with WHBV, up to 28 days of telbivudine treatment produced consistent, multilog reductions in circulating serum WHBV DNA levels.¹

In vitro toxicological assessments produced no adverse findings.¹⁻³ The 50% cytotoxic concentration (CC_{50}) of telbivudine in 2.2.15 cells was >2000 μ M, indicating an excellent therapeutic index in cell culture.³ Other in vitro results suggest that telbivudine is unlikely to be associated with hematologic or mitochon-

drial toxicities, peripheral neuropathy, or myopathy.³ Mutagenic test results were negative.¹

Acute, subchronic, and chronic toxicology studies did not identify any preclinical safety issues for telbivudine.^{1,2} In acute and subchronic (28-day) toxicity studies conducted in rats and monkeys with daily doses up to 2000 mg/kg, no treatment-related clinical abnormalities were observed.¹ Chronic toxicity studies (6 months in rat; 9 months in cynomolgus monkeys), at doses up to 1000 mg/kg/d, indicated no significant clinical, biochemical, or anatomical pathological changes in the treated animals.¹

Preclinical pharmacological studies conducted in cynomolgus monkeys following oral and intravenous doses showed that telbivudine was well absorbed with an oral bioavailability of 68%.⁴ Renal clearance appeared to be the major pathway for telbivudine elimination.⁴

A recently completed phase 1/2 dose-escalation trial evaluating the pharmacokinetics, safety, and antiviral activity of telbivudine in patients with chronic HBV infection treated for 4 weeks with daily doses of telbivudine ranging from 25 to 800 mg demonstrated that telbivudine exhibited profound dose-related anti-HBV activity. At the end of 4 weeks of treatment, the median reduction from baseline in serum HBV DNA

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level was approximately $4 \log_{10}$ or 99.99%, which was observed at doses in the 400- to 800-mg/d range. Telbivudine 600 mg/d was selected for large-scale clinical trials based on dose-response analyses. Plasma pharmacokinetics of telbivudine was dose proportional through 800 mg. Telbivudine was well tolerated at all dose levels. No serious adverse events and no dose-limiting toxicities were reported. There were no significant clinical or laboratory abnormalities throughout the study.⁵

Telbivudine is intended to be administered daily by oral administration to patients with chronic HBV infection. It is therefore important to determine whether food intake would affect the absorption of the drug. This report provides detailed pharmacokinetic and statistical analyses of telbivudine administered to healthy subjects as a single dose of 600 mg with and without food according to a crossover design.

MATERIALS AND METHODS

Study Population

This study was conducted in accordance with good clinical practice procedures and US Food and Drug Administration regulations. Approval for the study was obtained from the Novum Independent Institutional Review Board (Pittsburgh, Pa). All subjects gave written informed consent after the nature of the study was fully explained. Healthy nonsmoking subjects, male and female, between 18 and 75 years of age and within 15% of normal body weight for their size and frame were eligible for the study. There had to be no evidence of clinically significant abnormalities on medical history, physical examination, 12-lead electrocardiogram, or clinical laboratory testing during screening. All prescription and over-the-counter medications were to be discontinued 3 days prior to study drug administration except for systemic contraceptives. Female subjects had to be surgically incapable of pregnancy or postmenopausal for at least 1 year or practicing a double-barrier method of contraception plus systemic contraceptives. Pregnant or lactating female subjects were excluded from the studies. Subjects were also excluded if they had a history of clinically important disease that, in the opinion of the investigator, may put the patient at risk because of participation in the study; tested positive for HIV, hepatitis C virus, or HBV; tested positive for drugs of abuse or alcohol; or had participated in a clinical study or donated blood or blood products within 30 days prior to study drug administration.

Study Design

This was a single-dose, open-label, randomized, 2-period, crossover study conducted from April 17, 2002, to June 4, 2002, at the clinical research facility of Novum Pharmaceutical Research Services (Houston, Tex). Twenty-four healthy subjects meeting the inclusion criteria were randomized to receive by oral administration a single dose of 600 mg telbivudine as 3×200 -mg tablets on study day 1 and day 8, respectively, according to the following sequences: fasted then fed and fed then fasted. Subjects were required to remain in the clinical research center during dosing and sampling and released for the washout period separating the 2 doses. For dosing under fasting conditions, all subjects were fasted for 10 hours prior to dosing, and food was allowed 4 hours after dosing. For dosing under fed conditions, telbivudine was administered immediately (within 5 minutes) following a high-fat and high-calorie test meal consisting of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz of whole milk, which derived approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

Blood Sample Collection

Serial blood samples were collected into heparin-containing Vacutainer tubes prior to and after dosing on study day 1 and day 8 at the following time points: 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, and 32 hours. Plasma was obtained by centrifugation and stored at -20°C or below until analysis. Telbivudine has been shown to remain stable for at least 1 year under the above storage conditions. The short-term stability of telbivudine in plasma has been documented when spiked samples were subject to 3 freeze and thaw cycles (-22°C to room temperature) and storage at room temperature for more than 26 hours.

Plasma Sample Analysis

Plasma samples were analyzed for telbivudine concentration using a validated high-performance liquid chromatography (HPLC) method with mass-spectrometric (MS/MS) detection. Briefly, to 100 μL of calibration standards (10 to 5000 ng/mL), quality controls (QCs; 30 to 4000 ng/mL), and unknown plasma samples were added 40 μL of internal standard (β -L-2'-deoxyadenosine (LdA) at 650 ng/mL) containing thymidine phosphorylase (EC 2.4.2.4; Sigma Chemical Co, St. Louis, Mo; $>1 \text{ U/mL}$). The mixture was vortexed

thoroughly and incubated at 37°C for 1 hour to digest any endogenous thymidine. After incubation, acetonitrile (200 µL) was added to precipitate protein. Samples were centrifuged, and the supernatant was transferred into HPLC injection vials. Reverse-phase chromatography was performed on a TSK-GEL Amide-80 column (4.6 × 150 mm, 5 µ; Tosoh Bioscience, Montgomeryville, Pa). Elution was carried out isocratically at 1 mL/min with a mobile phase of 90:10 (v/v) methanol:25 mM ammonium formate (pH 3.5). Under these conditions, the retention time was approximately 1.68 and 1.73 minutes for telbivudine and LdA, respectively. Telbivudine and LdA were monitored using a PE Sciex API 3000 MS/MS analyzer at mass transition of 243.0 to 127.1 m/z and 252.0 to 136.0 m/z, respectively. This assay has a lower limit of quantitation (LOQ) of 10 ng/mL, with a calibration curve range from 10 to 5000 ng/mL. Intra- and interday precision (percentage coefficient of variation) and accuracy (percentage deviation) ranged from 2.3% to 5.6% and -4.2% to 1.4%, respectively, based on QC samples ranging from 30 to 4000 ng/mL.

Safety Evaluation

Safety and tolerability were evaluated through adverse events (AEs) reported by the investigators and subjects on the basis of clinical laboratory measurements (blood chemistry, hematology, urinalysis, and liver functions), 12-lead electrocardiogram, physical examination, and vital signs. AEs were assessed by the investigators with regard to severity (mild, moderate, severe, and life threatening) and relationship to study treatment (reasonably or possibly related, not reasonably or possibly related).

Pharmacokinetic Analysis

The plasma concentration-time data of telbivudine obtained on days 1 and 8 were analyzed by model-independent approaches. The maximum plasma drug concentration (C_{\max}) and time to C_{\max} (T_{\max}) were directly obtained from the plasma concentration-time profiles. The observed elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$, where K_{el} is the absolute value of the slope of the apparent terminal linear phase of the natural log (ln)-transformed plasma drug concentration-time curve estimated using linear regression. The area under the plasma concentration-time curve from time 0 to t (AUC_{0-t}), where t is the time of last measurable sample, was calculated according to the linear trapezoidal rule. The AUC from time 0 to infinity

($AUC_{0-\infty}$) was estimated as $AUC_{0-t} + C_t/K_{el}$, where C_t is the plasma concentration of the last measurable sample. Apparent total plasma clearance (CL/F) was calculated as $\text{dose}/AUC_{0-\infty}$ and apparent total volume of distribution (V_d/F) as CL/K_{el} .

Statistical Analysis

Principal pharmacokinetic parameters underlying extent of plasma exposure (C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$) and elimination ($t_{1/2}$) were ln-transformed. The analysis of variance model included the following factors: subject, treatment, and period, and analysis was performed using the GLM procedure in SAS (version 8.0; SAS Institute Inc, Cary, NC). Results for C_{\max} , AUC, and $t_{1/2}$ were reported as 90% confidence intervals (CIs) about the ratio of the geometric least-squares (LS) means of the pharmacokinetic measures between fed (test) and fasted (reference) treatment. The resulting confidence limits were transformed by exponentiation and reported on the original measurement scale. It was concluded that no significant food effect on telbivudine pharmacokinetics exists if the 90% CI on the ratio of geometric LS means was contained within the critical range of 80% to 125% for bioequivalence for C_{\max} and AUC. T_{\max} was analyzed using a Wilcoxon pairwise signed rank test.

RESULTS

Subjects and Data Analyzed

Twenty-four healthy subjects participated in the study. All subjects completed the study and were included in pharmacokinetic and safety evaluations. Table I summarizes subjects' demographic data. Of the 24 subjects, however, 13 had low but measurable telbivudine levels before dosing in the second period with a mean of 17.6 ng/mL (range, 10.3-41.6 ng/mL), representing only 0.6% of C_{\max} . Such a low residual predose exposure was considered trivial, and therefore carryover effect was not analyzed.

Effect of Food on the Pharmacokinetics of Telbivudine

As shown in Figure 1, mean plasma pharmacokinetic profiles of 600 mg telbivudine administered orally with and without food are virtually superimposable. Mean principal pharmacokinetic parameters including C_{\max} , T_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, as well as $t_{1/2}$, as summarized in Table II, are comparable when telbivudine

Table I Subject Characteristics at Baseline (N = 24)

Characteristic	Mean	SD	n
Age, y	31.6	10.7	
Weight, kg	67.4	8.3	
Height, cm	170.1	8.8	
Gender			
Male			12
Female			12
Race			
Caucasian			6
African American			12
Hispanic or Latino			6

was administered under fed and fasting conditions. Ratios of geometric LS means of C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$ (fed vs fasted) were 103.8%, 107.2%, 106.4%, and 95.9%, respectively, with surrounding 90% CIs contained within the 80% to 125% critical range for equivalence (Table II). A Wilcoxon pairwise signed rank test indicated that T_{\max} was not affected by food intake ($P > .7$). No delay in telbivudine absorption was observed when telbivudine was administered under fed conditions. C_{\max} was reached at a median T_{\max} of 3.0 hours (median difference = 0 hours; 95% CI, -1 to 0 hours) under fasting and fed conditions. Values of other derived parameters including CL/F and V_d/F were also comparable when telbivudine was administered with and without food (Table II). Therefore, intake of a high-fat and high-calorie meal immediately prior to oral dosing did not alter plasma pharmacokinetics of telbivudine, and telbivudine can be administered with no regard to the timing of food.

Safety Evaluation

Safety results from all 24 subjects were evaluated. Telbivudine administered as a single dose of 600 mg in 2 periods was well tolerated by all subjects under fasting and fed conditions. A total of 42 AEs were reported by 19 (79.2%) of the 24 subjects. AEs reported during the study were all mild. Headache (12.5%), somnolence (16.7%), and decrease in body temperature (25%) were the most common AEs reported. Three subjects (12.5%) had an increase in blood triglycerides at the end of the study (210-278 mg/dL) compared to baseline (78-135 mg/dL), which became normal (94-123 mg/dL) upon reexamination 1 to 3 weeks following the end of study treatment. No serious AEs occurred during the conduct of the study, and no subjects dis-

continued from the trial due to AEs. There were no treatment-related trends observed regarding clinical laboratory parameters, vital sign measurements, or physical examination findings with respect to subject safety. Except for headache, all other AEs were considered by the investigator as unlikely to be related to telbivudine.

DISCUSSION

Telbivudine is an orally bioavailable nucleoside antiviral that is being developed as a once-daily treatment for patients with chronic HBV infection.¹ An oral daily regimen would be more convenient if the drug could be taken with no food restriction, as it was previously shown that convenience of dosing regimen positively affects compliance and may improve treatment outcome.⁶

The current study was conducted in healthy volunteers rather than in HBV-infected patients because 2 single doses of the drug, which is typical for a food-effect study, are, however, not expected to result in continuous intracellular exposure of the active triphosphate of telbivudine. The use of healthy volunteers in this food effect study was further deemed appropriate based on comparable pharmacokinetic findings from this study to a previous dose-escalation trial in HBV-infected patients (X. J. Zhou et al, unpublished data, 2005), with the exception that half-life was underestimated in the dose-escalation study because of a short sampling period of only 8 hours. This short sampling period allowed only for the observation of the initial post-peak distribution/elimination phase. The current study with blood samples up to 32 hours revealed the existence of a second elimination phase with a $t_{1/2}$ of 17 hours; more recent studies with prolonged sampling to 120 to 168 hours had a more accurately estimated terminal $t_{1/2}$ approximating 40 hours (unpublished data). The long plasma half-life of telbivudine is responsible for the observed low but measurable predose concentrations prior to the second period dose in this study. These residual predose levels represented <1% of C_{\max} and therefore had no impact on the food-effect analysis. A sampling period of 32 hours proved adequate for food effect evaluation of telbivudine since AUC_{0-t} represented approximately 90% of $AUC_{0-\infty}$ (based on data in Table II) and C_t , averaging about 0.08 $\mu\text{g/mL}$, represented only 3% of C_{\max} .

The long plasma terminal $t_{1/2}$ of telbivudine is consistent with the long intracellular $t_{1/2}$ (>15 hours) of its active triphosphate observed in HepG2 cells.⁷ While the relevance of plasma to intracellular half-lives remains to be elucidated, those long half-lives are reflec-

Table II Summary of Telbivudine Plasma Pharmacokinetic Parameters in Healthy Subjects After Oral Administration of a Single Dose of 600 mg Under Fasting and Fed Conditions^a

Parameter	Fasted (n = 24)	Fed (n = 24)	Geometric LS Mean Ratio, % ^b	90% CI
C _{max} , µg/mL	2.7 ± 0.70	2.8 ± 0.70	103.8	96.4 to 111.9
AUC _{0-t} , µg•h/mL	19.6 ± 5.4	20.8 ± 4.7	107.2	98.0 to 117.2
AUC _{0-∞} , µg•h/mL	21.8 ± 5.5	23.0 ± 5.0	106.4	98.6 to 114.8
t _{1/2} , h	17.3 ± 6.0	16.8 ± 5.9	103.8	96.4 to 111.9
T _{max} , h ^c	3.0 (1.0-6.0)	3.0 (2.0-4.0)	0	-1 to 0
CL/F, L/h	29.4 ± 8.4	27.3 ± 5.7		
V _d , L	750.0 ± 365.7	668.1 ± 304.6		

a. Values for pharmacokinetic parameters are presented as mean ± standard deviation unless otherwise indicated.

b. Based on ln-transformed parameters.

c. Nonsignificant (*P* = .7) by Wilcoxon pairwise signed ranked test. Results reported as median (range), median difference, and 95% CI.

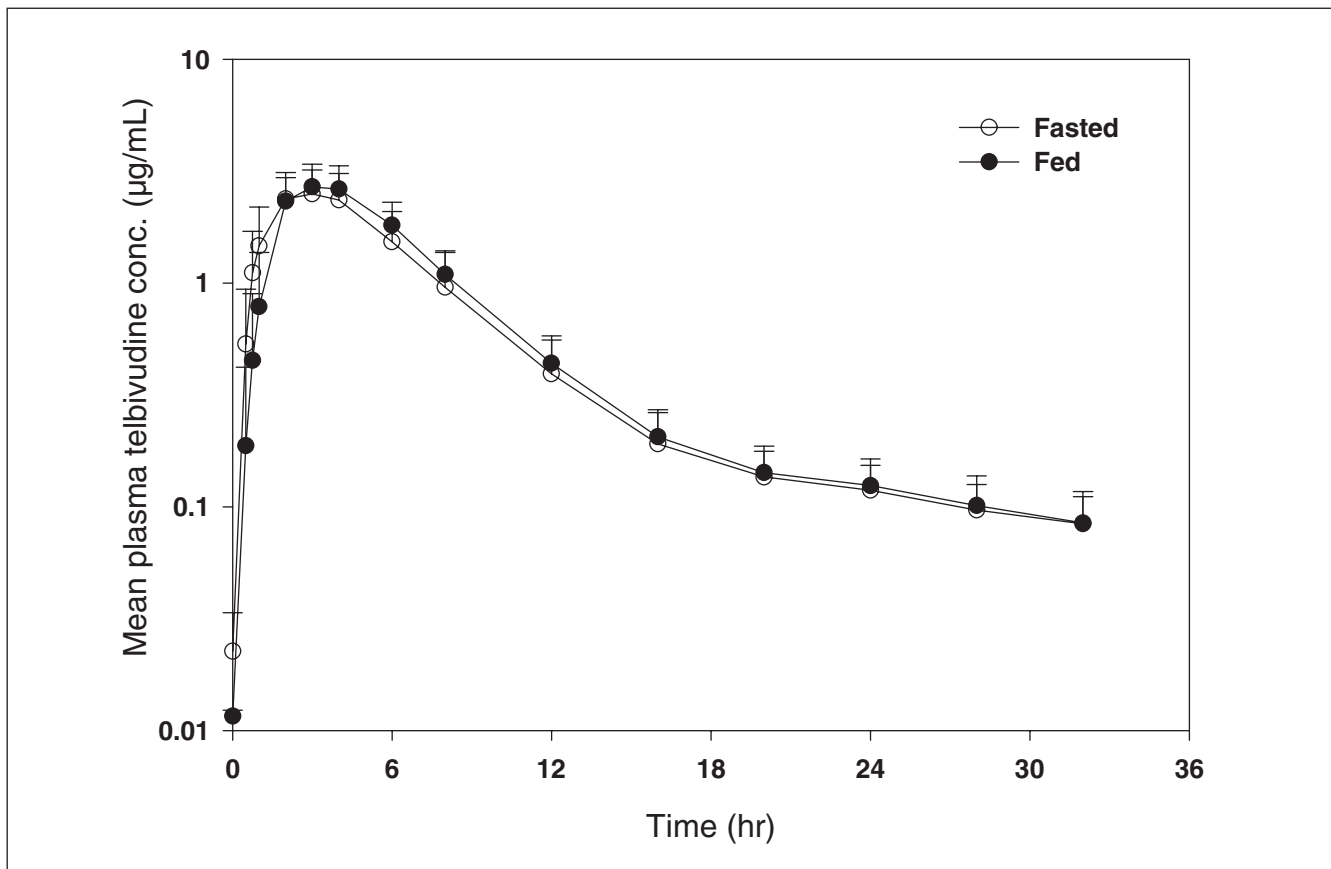


Figure 1. Mean (SD) single-dose plasma concentration-time profiles of telbivudine 600 mg after oral administration in healthy subjects under fasting (open circles) and fed (closed circles) conditions.

tive of sustained exposure and support the use of once-daily dosing of telbivudine.

Results from the present study conducted in healthy volunteers receiving 600 mg telbivudine under fasting

and fed conditions indicate that a high-fat and high-calorie meal ingested shortly before dosing does not appear to cause any obvious changes in the rate of absorption or the extent of plasma exposure of tel-

bivudine. After oral administration of a single dose in healthy subjects, telbivudine C_{max} was reached with a median T_{max} of 3 hours irrespective of fasting or fed conditions. Moreover, with a high-fat/high-calorie meal, telbivudine peak and overall exposure were comparable with data obtained under fasting conditions. Therefore, food did not delay telbivudine absorption or reduce its peak or overall exposure.

The absence of an effect of food on telbivudine absorption, likely to be associated with its physicochemical properties (ie, high solubility and permeability), makes this drug somewhat distinctive from other nucleoside antivirals currently used in the treatment of HBV and/or HIV infection. Food typically delays absorption and/or reduces C_{max} of nucleoside antivirals as previously reported for lamivudine (15%-47% decrease in C_{max} , ~1-hour delay in T_{max} , and AUC mostly unaffected),⁸⁻¹⁰ zidovudine (28%-73% decrease in C_{max} , ~0.6-1 hour delay in T_{max} , and up to 33% decrease in AUC),⁹⁻¹⁵ abacavir (28%-32% decrease in C_{max} , 38 minutes to 1 hour delay in T_{max} , and AUC unaffected),^{10,16} stavudine (46% decrease in C_{max} , ~1-hour delay in T_{max} , and AUC unaffected),¹⁷ and emtricitabine (29% decrease in C_{max} , AUC unaffected).¹⁸ While in most cases such an effect of food is considered clinically insignificant since overall plasma exposure (AUC) is little affected, food can significantly reduce absorption as is the case for the HIV antivirals didanosine (22%-61% decrease in C_{max} , up to 3-hour delay in T_{max} , and 19%-55% decrease in AUC)¹⁹⁻²¹ and zalcitabine (39% decrease in C_{max} , 2-fold increase in T_{max} , and 14% decrease in AUC)²² and, more recently, for the anti-HBV entecavir.²³ In the latter case, a standard high-fat meal delayed absorption and reduced 44% to 46% of C_{max} and 18% to 20% of AUC, requiring the drug to be taken in a fasted state.²³ The effect of food on the absorption of these antiviral nucleoside analogs is likely due to fat delaying gastric emptying, interfering with disintegration/dissolution processes, and/or reducing drug stability.

In conclusion, this study has clearly demonstrated that telbivudine 600 mg taken orally under fasting and fed conditions was bioequivalent with respect to pharmacokinetic parameters measuring absorption (C_{max} , T_{max} , and AUC). Telbivudine may therefore be taken without regard to the timing of meals.

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