Effect of Food on the Pharmacokinetics of 
(−) and (+) dOTC When Administered as an Oral Racemate

Patrick F. Smith, Alan Forrest, John M. Adams, and Charles H. Ballow

Significant advances in the treatment of the human immunodeficiency virus (HIV-1) have been made over the past decade. The development of combination drug regimens active against both the HIV-1 reverse transcriptase and protease enzymes has effectively altered the natural history of the disease. However, successful treatment remains limited due to important barriers such as the development of drug resistance, toxicity, patient adherence, and drug interactions. Newer agents that address these limitations are needed to further improve the treatment of this disease.

dOTC is a novel reverse transcriptase inhibitor of the 4′-thio heterosubstituted class of nucleoside analogues, with a 2′-deoxy-3′-oxa-4′-thiocytidine structure. Both enantiomers, (−) and (+) dOTC, have demonstrated pharmacological activity against the HIV-1 virus in vitro and remain active against HIV-1 clinical isolates that are resistant to lamivudine, zidovudine, saquinavir, and indinavir. An early clinical study with the racemic mixture demonstrated potent activity in antiretroviral naive patients treated with 7 days of monotherapy. Currently, the (−) enantiomer (SPD-754, formerly BCH-10618) is under clinical development and may offer significant advantages over currently available nucleoside analogues.

The effect of food on the pharmacokinetics of antiretroviral compounds remains an issue with significant clinical implications. Currently, there are agents available that must be administered with meals, and others must be taken on an empty stomach, which may lead to complicated medication regimens. Newer
agents that can be taken without regard to food result in improved adherence, leading to a decreased risk of resistance and improved therapeutic outcomes. The purpose of the present study was to determine the effect of food on the pharmacokinetics of both dOTC stereoisomers, (-) and (+) dOTC, when administered as a racemic mixture.

METHODS

The study protocol was approved by the institutional review board of Millard Fillmore Health Systems. Written informed consent was obtained for each subject prior to study participation. Racemic dOTC was supplied by BioChem Pharma, Inc. (Laval, Canada).

Study Design

This was a randomized, open-label, single-dose, complete crossover study in healthy, non-HIV-infected adult male volunteers. Inclusion criteria required subjects to be nonsmokers between 18 and 50 years of age and weight $\geq 50$ kg and within 15% of ideal body weight. A negative urinal drug screen was also required. Exclusion criteria included a clinically relevant abnormality identified during the screening physical or laboratory examination; history of a significant cardiac, renal, hepatic, neurologic, or hematologic abnormality; a history of alcohol or drug abuse within 6 months of the study; treatment with an investigational drug within 30 days or use of any prescription or nonprescription drug within 6 months of the study; treatment with an investigational drug within 30 days or use of any prescription or nonprescription drug within a week prior to the administration of study medication; or donation of 1 unit of blood within 60 days prior to the first dose of study medication.

Subjects each received 800 mg racemic dOTC orally with 240 ml tepid water in two study periods separated by at least 1 week. Prior to each dose, subjects were admitted to the Clinical Research Center and maintained in the fasted state for at least 10 hours prior to dosing, except for water. In the fasting study period, subjects remained in the fasting state for at least 5 hours after each dose of study drug. In the fed study period, subjects were given a standard Food and Drug Administration (FDA) high-fat breakfast equivalent to 1020 calories (58 g carbohydrates, 33 g protein, 58-75 g fat). The meal consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 10 grams of butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The meal was completely consumed within 20 minutes, and dOTC was administered 10 minutes after meal consumption.

Blood samples (5 ml) were drawn prior to dosing (time 0) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours after dosing for analysis of (-) and (+) dOTC concentrations. Blood samples were immediately separated at approximately 4°C by centrifugation, and plasma was stored at approximately -20°C until analyzed by a validated assay procedure. The (-) and (+) enantiomers were separated using a solid-phase extraction cartridge. Plasma concentrations of (-) and (+) dOTC were measured by reverse-phase high-performance liquid chromatography with UV detection, using 2',3'-dideoxycytidine as an internal standard. For assay accuracy, (-) dOTC had a coefficient of variation (CV) range of 2.4% to 4.5% for interassay and 1.0% to 4.2% for intra-assay variability. For (+) dOTC, the CV range was between 2.4% and 3.9% for interassay and between 1.3 and 2.7% for intra-assay variability. The lower limit of quantitation for both enantiomers was 3.0 ng/ml. The assay was linear over the range of 3.0 to 1000 ng/ml for both enantiomers. Concentrations above 1000 ng/ml were diluted to obtain a concentration within the linear portion of the calibration curve and reanalyzed. Quantitation was performed using the peak height ratio method, and samples were assayed in random order. Additional details of the assay methodology have been previously described.

Pharmacokinetic Analyses

Pharmacokinetic parameters were determined by standard noncompartmental methods. The terminal elimination rate constant ($\lambda_z$) was determined by linear regression of data points within the terminal elimination phase. Area under the curve (AUC) was determined by the standard linear trapezoidal method, with $\text{AUC}_{24-\infty}$ computed as the sum of the first 24 hours ($\text{AUC}_{0-24}$) and $\text{AUC}_{24-\infty}$. $\text{AUC}_{24-\infty}$ was calculated as $C_{\text{last}}/\lambda_z$, where $C_{\text{last}}$ was the final measured serum concentration. The maximum observed plasma concentration ($C_{\text{max}}$) and time of $C_{\text{max}}$ ($t_{\text{max}}$) were determined by visual inspection of the data.

Statistical Analysis

Comparisons of fed and fasted study periods were accomplished using the Wilcoxon signed rank procedure. In addition to testing for statistical differences between study periods, strength of bioequivalence between fed and fasted periods was assessed. The approach involves the use of the two one-sided tests procedure to analyze the bioavailability variables ($\text{AUC}_{0-\infty}$ and $C_{\text{max}}$). A 90% equivalence interval (EI) for the ratio of fed to fasted geometric means was con-
structured. Equivalence was declared between fed and fasted study periods when the 90% EI fell within the interval of 0.80 to 1.25.

RESULTS

Twelve male subjects completed the study with a mean (CV%) age of 30.5 (29.9) years, weight 80.3 (10.4) kg, and serum creatinine 0.95 (21.3) mg/dl. All oral doses were well tolerated by the subjects, and no adverse events were reported.

A summary of pharmacokinetic parameters is provided in Table I, and mean plasma concentration-time curves for the fasted and fed study periods are illustrated in Figure 1. By inspection, the concentration-time profiles for each enantiomer are similar but are delayed by food. The mean $C_{\text{max}}$ values were approximately 10% lower and the mean AUC 10% higher when administered with food. However, neither $AUC_{0\rightarrow\infty}$ ($p \geq 0.10$) nor $C_{\text{max}}$ ($p \geq 0.35$) differed significantly between fed and fasted study periods for either enantiomer. The $t_{\text{max}}$ of each enantiomer was delayed by coadministration of a high-fat breakfast (medians were 0.6-0.7 h longer, $p \leq 0.02$). Intersubject variability was very low, with CV% ranging from 20% to 24% for AUC and 14% to 28% for $C_{\text{max}}$.

Tests of equivalence between fed and fasted study periods on $AUC_{0\rightarrow\infty}$ and $C_{\text{max}}$ for (+) dOTC are also reported in Table I. The fed and fasted study periods were equivalent in $AUC_{0\rightarrow\infty}$. The percentage of $AUC_{0\rightarrow\infty}$ extrapolated beyond the observed data was less than 10% in all subjects (calculated as $100\% \times AUC_{24\rightarrow\infty}/AUC_{0\rightarrow\infty}$). Values of the 90% confidence interval for $C_{\text{max}}$ of both enantiomers also fell within the required range of 0.80 to 1.25 and therefore also meet the requirements for bioequivalence. Clearly, the pharmacokinetics of (-) and (+) dOTC is not significantly affected by food when administered as a racemic mixture.

DISCUSSION

The current study has demonstrated that a high-fat meal has no clinically significant effect on the pharmacokinetics of either dOTC enantiomer. Values of AUC and $C_{\text{max}}$ were very consistent within subjects in both the fed and fasted study periods, as each changed by less than 10% when administered with a high-fat meal. Intersubject variability in these parameters was also very low, indicating a consistent absorptive process that is not significantly altered by food.

The effect of food on the bioavailability of other nucleoside analogues has been investigated previ-
ing in a reduction in drug exposure. A study with zido-
dovudine compared the effect of food on the adminis-
tration of 100 mg and 250 mg oral doses, finding a 37% 
and 73% reduction in Cmax, respectively. AUC was also 
reduced by 14% and 33% with the 100 mg and 250 mg 
doses, respectively. The investigators of this study and 
those of a subsequent study\textsuperscript{12} both concluded that 
zidovudine should not be taken with food. Similarly, 
the bioavailability of didanosine has also been found to 
be reduced when administered concurrently with meals.\textsuperscript{11}

Lamivudine and stavudine are available nucleoside 
reverse transcriptase inhibitors that have met the FDA 
criteria for bioequivalence when administered with 
food and may be taken without regard to meals.\textsuperscript{7,8} Interestingly, the disposition of (–) and (+) dOTC appears to 
be much less affected by food than either of these 
agents, with the mean Cmax decreased and AUC in-
creased by approximately 10% or less. These relatively 
small changes in both Cmax and AUC are significantly 
less than those reported for the other nucleosides. Decreases in Cmax when administered with food, have 
been reported to be approximately 50% with zidovu-
dine,\textsuperscript{12} 39% with zalcitabine,\textsuperscript{9} 54% with stavudine,\textsuperscript{8} and 47% with lamivudine.\textsuperscript{7} These relatively large dif-
fferences in Cmax values observed with other nucleo-
sides might be important if pharmacodynamic evalua-
tions can demonstrate a relationship between Cmax and 
drug efficacy or toxicity.

The current study has demonstrated that food has no 
significant effect on the pharmacokinetics of either 
dOTC enantiomer when administered as a racemic 
mixture. This finding may allow this agent to be com-
bined with other antiretroviral agents in regimens that 
are less complex, thereby promoting adherence. It 
should be noted that this study was conducted in 
healthy volunteers, rather than HIV-infected individu-
als, and confirmation of these findings in the targeted 
patient population may be important.

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