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A Study Examining the Pharmacokinetics of Abacavir and the Intracellular Carbovir Triphosphate (GSK Protocol CNA10905)

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Introduction

Abacavir (ZIAGEN) is a highly potent nucleoside reverse transcriptase inhibitor with activity against HIV-1. Clinical studies have demonstrated its effectiveness in HIV-infected patients in combination with other antiretrovirals as part of HAART.

Abacavir has a short plasma half-life of about 1.5 hours. Studies on the active moiety, intracellular carbovir triphosphate (CBV-TP) are discordant. In an *in vitro* study examining the intracellular anabolism of abacavir to CBV-TP in CEM cells, the CBV-TP half-life was 3.3 hours. However, two recent reports by Kewn et al[1] and Harris et al[2] demonstrated a prolonged intracellular CBV-TP profile with a half-life greater than 15 hours in limited numbers of HIV-infected patients receiving abacavir. Both studies used a template primer binding assay performed by Dr David Back's laboratory in Liverpool, UK.[3]

We sought to confirm the finding of Kewn et al[1] and Harris et al[2] using a GLP assay for intracellular CBV-TP to provide the pharmacologic basis of abacavir 600 mg once a day dosing.

Objectives

Primary Objective

To describe the intracellular pharmacokinetics (PK) of carbovir triphosphate (CBV-TP) at steady-state following administration of an abacavir 300 mg BID-containing regimen (ZIAGEN or TRIZIVIR) in HIV-infected patients.

Secondary Objective

To describe the PK of abacavir, and its relationship to triphosphate, at steady state following the administration of an abacavir 300 mg BID-containing regimen (ZIAGEN or TRIZIVIR) in HIV-infected patients.

Methods

HIV-infected patients (CD4 cell ≥300 cells/mm^3) on stable abacavir (300 mg BID) therapy as either ZIAGEN or TRIZIVIR (≥6 weeks) were enrolled. Other antiretroviral therapies were continued.

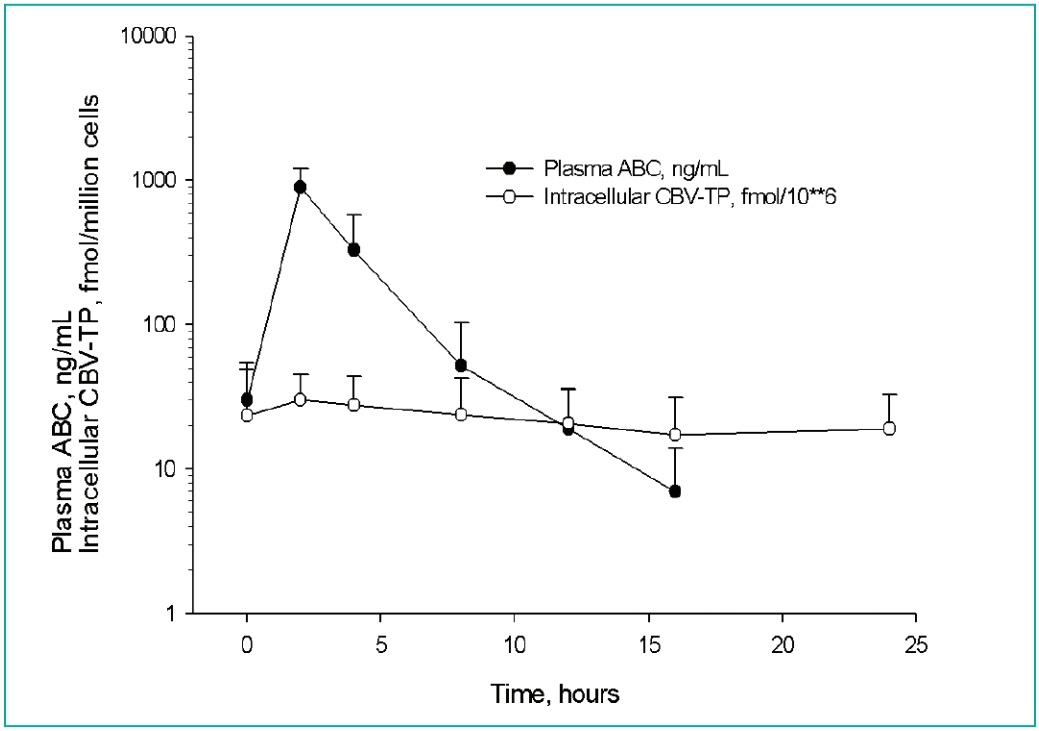
Patients were admitted to a CRC in the AM and the AM dose of abacavir was administered. The PM dose of abacavir was withheld. Patients on TRIZIVIR received COMBIVIR for their PM dose of zidovudine and lamivudine. PK samples were obtained at pre-dose (within 30 minutes prior to dose) and 2, 4, 8, 12, 16, and 24 hours after dosing in CPT tubes. The normal dosing regimen was restarted after the last PK sample. Plasma and PBMCs were harvested and processed and frozen at -20°C.

Plasma abacavir concentrations were determined using a method based upon solid phase extraction followed by LC/MS/MS analysis employing positive-ion Turbo ionspray ionization (lower limit of quantification, LLQ, 2.5 ng/mL for a 200 μL aliquot of human plasma).

Intracellular CBV-TP: PBMCs were assayed for CBV-TP using a method based upon anion exchange isolation, enzymatic hydrolysis to carbovir using alkaline phosphatase, with solid phase extraction clean-up followed by LC/MS/MS analysis employing positive-ion Turbo ionspray ionization (lower limit of quantitation, LLQ, 0.05 ng/mL for a 200 mL aliquot of human PBMC).

Non-Compartmental Pharmacokinetic Analysis was performed using WinNonlin™ Version 3.0 (Copyright ©1998-1999, Pharsight Corporation)

Figure 1 • Median Plasma Abacavir and Intracellular Carbovir Triphosphate Concentrations versus Time



- Twenty subjects were enrolled and completed the study. Nine subjects were on a current stable regimen containing ZIAGEN 300 mg BID and 11 subjects were on a current stable regimen containing TRIZIVIR BID.

- No drug-related adverse events, serious adverse events, abacavir hypersensitivity reactions, or deaths were reported during this study. No pregnancies occurred during the study. No subjects withdrew from this study due to an AE. A total of six adverse events were reported by four subjects. No adverse event was reported more than once. No clinically significant laboratory abnormalities were reported. No vital signs, ECG, or physical examination results were recorded as AEs.

Table 1 • Plasma Abacavir Pharmacokinetics

Parameter	Geometric Mean	95% CI
AUC_{0-24}, µg.h/mL	2.56	2.13-3.06
$C_{max,ss}$, µg/mL	0.88	0.75-1.03
$t_{max,ss}$, h	2.00	2.00-3.92
$t_{1/2}$, h	2.59	2.04-3.29

Table 2 • Intracellular Carbovir Triphosphate Pharmacokinetics

Parameter	Geometric Mean (N = 20)	95% CI
$AUC_{0-24,ss}$, fmol.h/10^6 cells	252.78	190.05-336.21
$C_{max,ss}$, fmol/10^6 cells	29.66	22.07-39.86
$t_{1/2}$, h	20.64	16.39-25.99
$C_{avg\ 0-tau}$, fmol/10^6 cells	21.07	15.84-28.02
$C_{tau,ss}$ (C_{12}), fmol/10^6 cells	16.56	14.24-27.43
C_{24}, fmol/10^6 cells	14.94	10.59-21.06

- The observed plasma abacavir pharmacokinetics were similar to those previously observed in HIV-infected patients.

- The intracellular CBV-TP concentration time profile demonstrated a flat terminal curve from approximately 8-12 hours through 24 hours. This resulted in a prolonged terminal half-life, geometric mean 20.64 hour. The 95% CI of geometric mean for $C_{max,ss}$ was in the range of 22-40 fmol/10^6 cells.

Discussion

- The prolonged CBV-TP half life observed *in vivo* is much longer than previously observed in *in vitro* studies (20.64 h vs 3.3 h) and may be due to a saturation step and pooling of precursors (CBV-MP or CBV-DP).

- CBV-TP concentrations were lower in this study compared to those reported previously.[1,2] This may be due to several factors including the small number of subjects in the two earlier studies, differences in cell processing, and differences in assay methodology (non GLP template primer binding assay versus GLP specific LC/MS/MS).

- Intracellular CBV-TP concentrations were on average approximately 2-fold higher than the reported Ki value for dGTP into DNA by HIV-1 RT of 21 nmol/L, Daluge et al,[3] throughout the 24 h interval, with concentrations of ~20 fmol/10^6 cells (40 nmol/L).

Conclusions

- These intracellular pharmacokinetics of CBV-TP are similar to those described by Kewn et al and Harris et al. The long half life of CBV-TP of 20.64 hours provides pharmacological support for the administration of abacavir once daily. Clinical studies are evaluating the use of abacavir 600 mg once a day.

References

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2. Harris M, Jutha S, Back D, et al. *8th Conference on Retrovirus and Opportunistic Infections*. Feb 4-8 2001. Chicago, IL, USA. Abstract No. 746.
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