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Penetration of the Nucleoside Analogue Abacavir into the Genital Tract of Men Infected with Human Immunodeficiency Virus Type 1

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The male genital tract is considered an anatomical reservoir during therapy for human immunodeficiency virus infection, because the blood-testis barrier may prevent antiretroviral drugs (e.g., the protease inhibitors ritonavir, saquinavir and nelfinavir) from entering the male genital tract. To our knowledge, there are currently no available data on the penetration of the nucleoside analogue abacavir into the male genital tract. Our report shows that abacavir has good penetration into the male genital tract.

Potent antiretroviral therapy can decrease concentrations of HIV type 1 (HIV-1) RNA in plasma and semen [1, 2]. However, the decrease in HIV-1 RNA concentrations and the evolution of virus in semen during therapy can show discordance with plasma, indicating compartmentalization of the virus [3, 4]. The poor penetration of some antiretroviral drugs into the male genital tract can contribute to the different viral dynamics in this area [5]. Available data on concentrations of nucleoside analogue reverse-transcriptase inhibitors (NRTIs) in semen show that zidovudine (zdv), stavudine (d4T), and lamivudine (3TC) penetrate well into the male genital tract [6, 7]. We investigated the penetration of the NRTI abacavir (ABC) into the male genital tract because, to our knowledge, no data on the subject currently exist.

Twelve men infected with HIV-1 who were treated with zidovudine (or d4T), 3TC, ABC (300 mg b.i.d.), nevirapine, and indinavir participated in this study [8]. Patients had no signs or symptoms of genital infection. At weeks 8 and 24, serial blood samples were collected by venapuncture to investigate the pharmacokinetic profile of ABC. Serum samples were obtained by centrifugation done at 4°C for 20 min at 1600 g. On the same day that blood samples were collected, semen samples were obtained by masturbation 0–2 hours before drug ingestion. Within 2–4 h after collection, semen samples underwent centrifugation at 1200 g for 10 min to obtain seminal plasma samples. All samples were stored at −70°C until analysis was done. ABC concentrations in blood serum and seminal plasma samples were measured using a high-performance liquid chromatographic procedure [9]. ABC concentrations in seminal plasma samples were assessed after the samples underwent 1:3 dilution with blank human heparinized plasma. The lower limit for quantification of ABC in blood serum and seminal plasma samples was 20 ng/mL and 60 ng/mL, respectively.

For ABC, the serum concentration versus time profiles are depicted in figure 1. Peak and trough concentrations of ABC (the highest observed concentration and the concentration observed 12 h after drug ingestion, respectively) in serum samples were not significantly different at weeks 8 and 24 ($P = .3$ and $P = .7$, respectively; Wilcoxon rank sum test). The median (interquartile range) peak concentration of ABC was 1223 ng/mL (925–2051 ng/mL). Only 5 of 24 trough concentrations showed detectable ABC concentrations, with concentrations ranging from 48 to 354 ng/mL.

For analysis of ABC concentrations in semen samples, a minimum of 0.5 mL of seminal plasma was required; this amount could be obtained at 18 of 24 sampling time points. ABC was detected in 8 of 18 semen samples, with concentrations ranging from 141 to 1819 ng/mL (figure 1). The differences in ABC concentrations in seminal plasma samples at the end of a dosing interval may be explained by individually determined differences in penetration of ABC into the male genital tract or by differences in clearance of ABC from the male genital tract during the dosing interval. To investigate these hypotheses, we performed an additional study in which 4 patients were asked to provide semen samples at the time of drug ingestion (0 h) and 2 h after ingestion. ABC was detected in only 1 of 4 semen samples obtained before drug ingestion; however, it was de-
phorylation. The serum elimination half-life of ABC is relatively short (0.8–1.5 h) [11], a finding that is in agreement with the rapid decrease in ABC serum concentrations observed in this study. However, the half-life of the active triphosphate metabolite of ABC (CBV-TP) in PBMC has been demonstrated to be much longer (>12 h), resulting in therapeutic concentrations of CBV-TP throughout a dosing interval [12]. Because little is known about the phosphorylation of the NRTIs in semen, the clinical implications of the penetration of NRTIs into semen are unclear. However, we have shown that ABC penetrates into the male genital tract, which is a prerequisite for antiviral potency in this compartment.

In conclusion, these findings show that there are differences in the penetration of NRTIs into the male genital tract and, soon after drug ingestion, reaches concentrations that exceed the in vitro inhibitory concentration (IC_{50}) for maximally susceptible HIV strains (70 ng/mL) 10–20-fold [10]. Under the assumption that the same percentage of protein binds in blood plasma and seminal plasma (i.e., 50% bound), the free drug concentration available for antiviral activity still exceeds the IC_{50} 5–10-fold. ABC concentrations were detected in 9 of 22 semen samples obtained at the end of the dosing interval. However, they were not detected in 13 of 22 semen samples obtained at the end of the dosing interval. This finding indicates that ABC can be rapidly cleared from seminal plasma and is in contrast with findings for seminal plasma concentrations of zidovudine and stavudine [6, 7].

In conclusion, these findings show that there are differences in the penetration of NRTIs into the male genital tract. It is important to note, however, that the NRTIs are pro-drugs, which exert their antiviral activity only after intracellular phosphorylation. The serum elimination half-life of ABC is relatively short (0.8–1.5 h) [11], a finding that is in agreement with the rapid decrease in ABC serum concentrations observed in this study. However, the half-life of the active triphosphate metabolite of ABC (CBV-TP) in PBMC has been demonstrated to be much longer (>12 h), resulting in therapeutic concentrations of CBV-TP throughout a dosing interval [12]. Because little is known about the phosphorylation of the NRTIs in semen, the clinical implications of the penetration of NRTIs into semen are unclear. However, we have shown that ABC penetrates into the male genital tract, which is a prerequisite for antiviral potency in this compartment.

Figure 1. Abacavir (ABC) concentration in seminal plasma and serum. Left (black circles), ABC concentration in seminal plasma samples 0–2 h before drug ingestion (ABC concentrations were detectable in 9 of 22 semen samples); open circles, ABC concentration in seminal plasma samples obtained from 4 patients 2 h after drug ingestion. Right, Median (interquartile range) serum concentration versus time profile of ABC for 12 patients infected with HIV type 1, as measured at weeks 8 and 24.

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