Pharmacokinetics and Tolerability of Tenofovir Disoproxil Fumarate 300 mg Once Daily: An Open-Label, Single- and Multiple-Dose Study in Healthy Chinese Subjects

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ABSTRACT

Background: Tenofovir disoproxil fumarate (TDF) has been approved worldwide for the treatment of adults with chronic hepatitis B and, in combination with other antiretroviral agents, HIV-1 infection. Although its use for the treatment of HIV has been approved by the Chinese State Food and Drug Administration, there are no data on the pharmacokinetic profile of TDF in Chinese individuals.

Objectives: This study aimed to investigate the pharmacokinetic properties and tolerability of TDF in healthy Chinese subjects.

Methods: This open-label, single- and multiple-dose study was conducted in healthy Chinese volunteers. Subjects received TDF 300 mg once daily, administered as a single dose (day 1) and multiple doses (days 4–10). Multiple plasma samples were collected over time, and the concentrations of TDF were determined using LC-MS/MS. Pharmacokinetic parameters were estimated using a noncompartmental model. Tolerability was determined using clinical evaluation and monitoring of adverse events (AEs).

Results: Fourteen volunteers were enrolled (7 men, 7 women; mean age, 24.6 years). TDF was rapidly absorbed; median T_{max} was 0.75 hour, and $t_{½}$ was ~21 hours with single dosing. The mean ratio of $AUC_{0-\tau}$ steady state/AUC_{0-24} single dose was 1.55. The pharmacokinetic properties of TDF were consistent between the single dose and multiple doses, and between men and women. No serious AEs were reported, and there were no discontinuations due to AEs.

Conclusions: There was an accumulation of approximately 55% in tenofovir exposure in healthy Chinese between multiple dose and single dose. TDF exhibited a pharmacokinetic profile similar to that of healthy Western subjects in a historical comparison. TDF was generally well tolerated in these healthy Chinese subjects. ClinicalTrials.gov identifier: NCT01480622. (*Clin Ther.* 2013;35:1884–1889)

Key words: LC-MS/MS, pharmacokinetics, tenofovir disoproxil fumarate, tolerability.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a potent and selective inhibitor of hepatitis B virus (HBV) DNA polymerase–reverse transcriptase in vitro.[1] It is also active against lamivudine-resistant HBV,[2–5] and has known activity against HBV both in patients with HBV monoinfection[6–9] and in patients co-infected with HIV-1 and HBV.[10,11]

TDF has been approved worldwide for the treatment of chronic hepatitis B (CHB) in adults and, in combination with other antiretroviral agents, HIV-1 infection. Although its use for the treatment of HIV has been approved by the Chinese State Food and Drug Administration, there are no data on the pharmacokinetic profile of TDF in Chinese individuals. To investigate the pharmacokinetic profile and potential differences in pharmacokinetic properties between Chinese and Western individuals, an open-

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label, single- and multiple-dose study in healthy Chinese subjects was conducted.

METHODS

This open-label, single- and multiple-dose study was conducted at a single center. The study protocol (Chinese National Registry code 2011L00048) was approved by an independent ethics committee, and the study was conducted in accordance with the guidelines for Good Clinical Practice recommended by the Chinese Food and Drug Administration[12] and with the ethical standards for human experimentation established in the Declaration of Helsinki.[13] All subjects provided written informed consent to participate in the study.

Inclusion and Exclusion Criteria

Healthy Chinese men and women aged 18 to 45 years and with a body mass index between 19 and 24 kg/m^2 were recruited. Eligible subjects met the following criteria: (1) *healthy,* defined as having unremarkable vital sign measurements, physical examination and ECG values, and negative HIV and hepatitis B/C statuses; (2) aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin $\leq 1.5 \times$ ULN; (3) in women, nonchildbearing potential or, if of childbearing potential, agreement to use ≥ 1 protocol-defined acceptable method of contraception (abstinence, oral contraceptive, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, double-barrier method); and (4) in men with a female partner of childbearing potential, abstinence or condom use and partner's agreement to use the contraceptive methods defined previously in female subjects of childbearing potential.

Subjects were excluded if they were using drugs or alcohol in excess (>7 drinks/wk in women or >14 drinks/wk in men; 1 drink = 5 fl oz of wine, 12 fl oz of beer, or 1.5 ounces of hard liquor); had taken part in a drug trial within the 12 weeks prior to screening; had donated blood or blood products >500 mL within the 8 weeks prior to screening; and/or were incapable of providing written informed consent, which included compliance with the requirements and restrictions listed on the consent form.

Study Drug Administration

The study included a screening visit, single- and multiple-dose periods, and a follow-up visit. Subjects who met the inclusion were admitted to the study center 1 day before the single-dose session and remained in-house until after the final pharmacokinetic sample had been collected. Subjects received a single TDF 300-mg tablet on day 1, followed by 7 days of repeated administration from days 4 to 10. All doses were administered after an ≥ 8-hour fast, with 240 mL (8 fl oz) of water, in the morning.

For the purposes of pharmacokinetic analysis, subjects were also required to fast for 4 hours after study drug administration on days 1 and 10. Meals were standardized during the whole study period. Water was allowed as desired except during the period from 1 hour before to 2 hours after study drug administration. During this period, water was restricted to the administered with drug.

The use of concurrent medications, including prescription and nonprescription drugs, vitamins, and herbal and dietary supplements, was disallowed within 7 days or 5 half-lives prior to the administration of the first dose of study medication;

Pharmacokinetic Assessment

Sample Collections

Blood samples (3 mL) were drawn throughout the study. Samples were collected before administration on days 1, 8, 9, and 10, and at 15, 30, 45, 60, 90, 120, and 180 minutes and 3, 4, 6, 9, 12, 15, 24, 36, 48, and 60 hours after administration on days 1 and 10. The collected blood samples were centrifuged at 1500*g* for 10 minutes at 4°C within 30 minutes, after which plasma was aliquoted into 2 polypropylene tubes and stored at –80°C (±10°C) until analyses were conducted.

Tenofovir Analyses

Plasma tenofovir concentrations were determined using a validated LC-MS/MS method at Wuxi AppTec, Shanghai, China. Tenofovir and its internal standard, tenofovir-D6 (Toronto Research Chemicals, Toronto, Ontario, Canada), were extracted using protein precipitation, and chromatographic separation was achieved on an Aquasil C_{18} Polar-RP column (Thermo Fisher Scientific, Waltham, Massachusetts [formerly Thermo Electron Corporation]). The MS method of tenofovir detection was similar to that used in previous studies.[14] The calibration curve ranged from 1.00 to 600 ng/mL of tenofovir in plasma. A correlation coefficient (r^2) >0.99 was desirable for all calibration curves. Intraday accuracy and precision were –6.0% to 4.0% and 1.0% to 10.2%, respectively, and interday accuracy and precision ranged from –4.7% to 1.0% and 2.3% to 8.2%.