Single-Dose Pharmacokinetic Properties, Bioavailability, and Tolerability of Two Lamivudine 100-mg Tablet Formulations: A Randomized Crossover Study in Healthy Chinese Male Subjects

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ABSTRACT

Background: Lamivudine is used in the treatment of HIV and chronic hepatitis B (HBV) infections. Since 1999, at least 2 million Chinese HBV patients have been treated with lamivudine, but there are limited studies on the pharmacokinetics and safety of the drug in Chinese populations.

Objective: This study was designed to assess the bioequivalence of a newly developed lamivudine tablet (test drug) and a branded lamivudine tablet (reference drug) in healthy Chinese male volunteers.

Methods: A single-center, single-dose, randomized, open-label, 2-period crossover study was conducted in 28 healthy Chinese male volunteers. Blood samples were collected up to 24 hours after the administration of oral lamivudine 100 mg in each period. Plasma lamivudine concentrations were analyzed by a validated LC–MS/MS method. Pharmacokinetic and bioavailability parameters were calculated. Adverse events (AEs) were recorded.

Results: There were no significant differences in mean (SD) pharmacokinetic parameters between the test and reference drugs, including C_{max} (1239 [328.9] ng/mL vs 1176 [341.5] ng/mL), AUC_{0-t} (4096 [599.1] ng · h/mL vs 4064 [678.2] ng · h/mL), and $AUC_{0-\infty}$ (4200 [607.7] ng · h/mL vs 4162 [672.2] ng · h/mL). The geometric mean test/reference ratios (90% CI) calculated for the log-transformed parameters were C_{max}, 1.06 (96.21–116.90); AUC_{0-t}, 1.01 (96.53–105.39); and $AUC_{0-\infty}$, 1.01 (96.81–105.16), all of which were within the acceptance limits for bioequivalence. No serious AEs were reported, and all mild AEs were recovered quickly without treatment.

Conclusion: These findings suggest that the test formulation of lamivudine 100 mg meets the FDA regulatory standards for bioequivalence with the reference formulation. Both formulations were well tolerated. (*Clin Ther*. 2013;▮:▮▮▮–▮▮▮) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: bioequivalence, Chinese male volunteers, lamivudine, LC–MS/MS, pharmacokinetics.

INTRODUCTION

Hepatitis B virus (HBV) is endemic and poses a major health problem in China.[1] Among the 350 million individuals infected with HBV worldwide, one third reside in China, with 130 million carriers and 30 million chronically infected.[2] Lamivudine, a potent nucleoside analogue reverse-transcriptase inhibitor, is used in the treatment of infections with HIV and chronic HBV. In 1998, lamivudine was approved by the US Food and Drug Administration (FDA) for the treatment of HBV, and in 1999 the drug entered the Chinese market. Since then, >2 million Chinese patients with HBV have been treated with lamivudine. As the first oral antiviral agent approved for the treatment of HBV, lamivudine is the only antiviral that has been reported in clinical trials to be well tolerated and potentially effective in treating both hepatitis B e antigen–positive and –negative, chronic HBV.[3]

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As an analogue of cytidine, lamivudine can inhibit both HIV and HBV reverse transcriptase after intracellular phosphorylation; its active 5′-triphosphate metabolite (lamivudine triphosphate, 3TC-TP) competes for incorporation into viral DNA to terminate its replication and growth. Additionally, 3TC-TP is a weak inhibitor of mammalian α-, β-, and γ-DNA polymerases, resulting in fewer effects on normal tissues.[4] Lamivudine is absorbed rapidly from the gastrointestinal tract after oral administration, with bioavailability >80% and a T_{max} of 0.5 to 1.5 hours. Coadministration of lamivudine with food results in a delayed T_{max} and a lower C_{max} (decreased by 47%), but the extent of absorption (based on the AUC) is not influenced.[5] After absorption, lamivudine is widely distributed into the total body fluid and can across the blood–brain barrier; the reported mean apparent volumes of distribution (V_d/F) of lamivudine following oral administration have ranged from 1.5 to 6.0 L/kg, irrespective of ethnicity.[5–8] Lamivudine is not metabolized by the cytochrome P450 3A isozyme, and is predominately cleared by renal excretion in an unchanged form (>70%). The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16–19 hours) that is significantly longer than that of the parent drug (5–7 hours).

With the growing prevalence of HBV in China, lamivudine as a highly effective anti-HBV agent has become increasingly popular. It is imperative to clarify the pharmacokinetic (PK) properties and safety profile of lamivudine in the Chinese population. However, previous bioequivalence and PK studies have mainly been performed in white, Hispanic, or Indian subjects.[7,9,10] The PK properties of lamivudine have also been studied when lamivudine was combined with other antiviral drugs, such as adefovir dipivoxil, zidovudine, and nevirapine.[6,9–11] Limited PK data are available from studies in Chinese subjects. Jiang et al[12] investigated the PK properties of lamivudine in healthy Chinese subjects using serum samples, not plasma samples, which have been used in most previous PK studies.[7,9–11] Therefore, their results cannot be used to directly compare the PK properties of lamivudine between ethnicities.

A newly developed lamivudine tablet has become available to Chinese patients. The present study was designed to assess the bioequivalence of the newly developed lamivudine 100-mg tablet (test drug, available as a generic) and the currently marketed lamivudine 100-mg tablet (reference drug) in Chinese male volunteers by determining the PK parameters after oral administration under fasting conditions. The test and reference drugs are of the same strength. In addition, the PK parameters were compared with those reported in studies in non-Chinese populations. The results from the present study will be beneficial in making treatment decisions with regard to the use of this drug in Chinese patients.

SUBJECTS AND METHODS

Study Design and Clinical Protocol

The study design and clinical protocol described herein were reviewed and approved by the ethics committee at the Jilin University First Affiliated Hospital–Clinical Research Institute, Changchun City, China. The clinical trial was conducted in accordance with the World Medical Congress Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from each of the participants. The clinical study was conducted at Jilin University First Affiliated Hospital–Frontage China Clinical Research Center, and the drug analysis was performed at Frontage Laboratories Company, Ltd (Shanghai, China).

This single-center, single-dose, randomized, open-label, 2-period crossover trial was designed to assess the bioequivalence of a test and reference formulation of lamivudine 100-mg tablets in healthy male subjects. Based on the $t_{½}$ values of lamivudine reported in previous studies, the treatment phases were separated by a minimum washout period of 7 days. This bioequivalence study compared the absorption rate and extent of the test formulation of lamivudine (qualified, expiration date, July 2014) to those of the branded reference formulation* (batch no. 12020039; expiration date, February 2015).

Participants

The participants enrolled in this study were recruited in Changchun City, China. They were deemed eligible for the study if they met all of the inclusion and exclusion criteria, as follows. Eligible subjects met the following inclusion criteria: healthy men between 10 and 40 years of age; body weight of at least 50 kg, with a body mass index of 19.0 to 24.0 kg/m^2; no

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