Current Therapeutic Research 77 (2015) 18–23

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/cuthre

Comparative Pharmacokinetic Study Among 3 Metformin Formulations in Healthy Mexican Volunteers: A Single-Dose, Randomized, Open-Label, 3-Period Crossover Study

Sandra Lucía Montoya-Eguía, DrC[1], Lourdes Garza-Ocañas, DrMed[1,*], Christian Tadeo Badillo-Castañeda, DrC[1], Eduardo Tamez-de la O, DrC[1], Teresa Zanatta-Calderón, DrC[1], Marco Vinicio Gómez-Meza, PhD[2], Humberto Garza-Ulloa, MC[1]

[1] *Departamento de Farmacología y Toxicología, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, CP 64460, Mexico*
[2] *Facultad de Economía, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, CP 64930, Mexico*

ARTICLE INFO

Key words:
Bioequivalence
generic formulations
metformin
Mexican population
pharmacokinetic

ABSTRACT

Background: Type 2 diabetes mellitus is the most common form of diabetes. Metformin is a first-line drug for its treatment. In Mexico, there are 34 generic formulations of metformin, so brand-generic substitutions and generic-generic substitutions are a common practice. Generic products are compared only with their brand-name equivalents and not with the same product made by other manufacturers.
Objective: Our aim was to establish whether 2 generic formulations of 500 mg metformin available on the Mexican market fulfill the criteria for interchangeability.
Methods: This single-dose, randomized-sequence, open-label, 3-period crossover study was conducted in 12 healthy subjects in compliance with the Declaration of Helsinki and International Conference on Harmonization guidelines. A validated HPLC procedure coupled with a spectrum mass detector were used to analyze the metformin concentration in plasma samples. All pharmacokinetic analyses were performed using WinNonlin Professional Software version 6.3 (Pharsight Corporation, Sunnyvale, California).
Results: Twelve healthy Mexican volunteers were enrolled in the study. Their mean age was 24.33 years and mean weight was 62.54 kg. The mean body mass index was 23.02. The values obtained for the test and reference formulations were: C_{max} 1163.5 (295.2) ng/mL for treatment A, 1184.6 (215.0) ng/mL for treatment B, and 1167.8 (176.8) ng/mL for treatment C. AUC_{0-t} was 6240.7 (1629.4) ng/mL/h for treatment A, 6433.7 (1249.8) ng/mL/h for treatment B, and 6567.1 (1145.5) ng/mL/h for treatment C. $AUC_{0-\infty}$ was 6837.3 (1618.5) ng/mL/h for treatment A, 6911.8 (1178.4) ng/mL/h for treatment B, and 7178.6 (1086.8) ng/mL/h for treatment C.
Conclusions: The test formulation 500-mg metformin tablets were bioequivalent to the reference formulation and to each other, according to the general laws of health care in Mexico.

Introduction

Diabetes mellitus is a complex chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control.[1] The worldwide prevalence of diabetes mellitus is currently estimated to be around 180 million and the World Health Organization predicts this number to double by 2030.[2] Type 2 diabetes mellitus is the most common form of the disease (affecting 90%–95% of persons with diabetes) and is characterized by an underlying insufficiency of insulin.[3,4]

Metformin is an orally administered antidiabetic drug from the biguanide class. It is recommended as a first-line drug for the treatment of type 2 diabetes mellitus.[5]

Metformin acts in the presence of insulin to increase glucose use and reduce glucose production, thereby counteracting insulin resistance. The effects of metformin include increased glucose uptake, oxidation and glycogenesis by muscle, increased glucose metabolism, and reduced hepatic gluconeogenesis.[4] Metformin is mainly absorbed in the small intestine and has an oral bioavailability of 60% under fasting conditions. Its plasma protein binding is negligible, and it is not metabolized by the liver. Metformin is 90% excreted unchanged in urine.[6]

* Address correspondence to: Dr. Lourdes Garza-Ocañas, Departamento de Farmacología y Toxicología, Facultad de Medicina, Universidad Autónoma de Nuevo León, Gonzalitos 235 Norte, Colonia Mitras Centro, Monterrey, Nuevo León, CP 64460, México.
E-mail address: logarza@live.com.mx (L. Garza-Ocañas).

http://dx.doi.org/10.1016/j.curtheres.2014.09.003

In Mexico, there are 34 generic formulations of metformin, so brand-to-generic substitution and generic-generic substitutions are a common practice.[7,8] It is important to keep in mind that generic products are only compared with their brand-name products and not with the same product made by other manufacturers.

Some studies[9–11] have warned about the lack of pharmacokinetic bioequivalence among generic drugs in the postmarketing setting. Therefore, based on these considerations, the aim of our work was to establish whether 2 generic formulations of 500 mg metformin available on the Mexican market fulfill the criteria for interchangeability.

Subjects and Methods

Materials

Metformin chlorhydrate USP was used for the study. HPLC-grade acetonitrile was purchased from Tedia High Purity Solvents (Fairfield, Ohio), HPLC-grade methanol and formic acid were purchased from Fermont (Monterrey, Nuevo León, Mexico). Deionized water was purchased from Laboratorios Monterrey (Monterrey, Nuevo León, Mexico).

Products evaluated

Reference A tested 500-mg Dabex tablets (Merck S.A. de C.V. Naucalpan de Juárez, Estado de México, México). Batch M33801, expires June 2017). Test B utilized 500-mg Pre-Dial tablets (Laboratorios Silanes S.A. de C.V. Toluca Estado de México, México). Batch 13LI07VI, expires November 2015. Test C utilized 500-mg Dimefor tablets (Siegfried Rhein Querétaro, Qro. México). Batch 310507, expires September 2015.

Study subjects

Twelve healthy adult (male and female) Mexican volunteers participated in the study. All were in good health based on their medical histories, complete physical examination, vital signs (eg, heart rate, systolic and diastolic blood pressure, and body temperature), and routine laboratory tests performed before and after the study (eg, complete blood count, blood chemistry, urinalysis, pregnancy test for women, renal and liver function tests, antibody testing for HIV, hepatitis B surface antigen, and hepatitis C virus). None had a history of any allergy to metformin and related compounds. Subjects did not receive any other medication during the study. All volunteers abstained from any xantine-containing food or beverages or alcoholic products for 48 hours before dosing and throughout the sampling schedule during each period.

Study design

The study was conducted in the Departamento de Farmacología y Toxicología, Facultad de Medicina, Universidad Autónoma de Nuevo León.

This is a single-dose, randomized-sequence, open-label, 3-period crossover study that was carried out under fasting conditions with a 1-week washout period.

Subjects were admitted and housed in our clinical pharmacology unit for 12 hours before the dose and were discharged 24 hours after the dose during each period. A single 500-mg tablet of the formulations was administered with 250 mL water after an overnight fast. A total of 15 venous blood samples (5 mL each) were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 16 hours. Serum was separated by centrifugation at 12,500 rpm for 10 minutes, and stored at –40°C until analysis.

A standardized breakfast and lunch were given at 4 and 8 hours, respectively, after medication administration.

Ethical considerations

The study protocol and the informed consent form were approved on May 6, 2014, by our institutional ethics and research committee (study No. FA14-001) and the study was conducted in accordance with the principles of the Declaration of Helsinki[12] and its amendments, the International Conference on Harmonization Guidelines for Good Clinical Practice,[13] and the general laws of health care in Mexico.[14] The order of treatment sequence (reference or test drugs) was randomized using Excel (version 2010, 2010, Microsoft Corp, Redmond, Washington).

Bioanalytic methods

The sample preparation process was accomplished by protein precipitation using acetonitrile. A 200-μL aliquot of each plasma sample was transferred to a polypropylene tube (Eppendorf, Hamburg, Germany), and 1000 μL acetonitrile was added. After brief vortex mixing, the tubes were centrifuged at 12,500 rpm for 10 minutes. Then the supernatants were evaporated to dryness under a nitrogen stream at 60ºC, reconstituted with 400 μL assay mobile phase, vortexed for 2 minutes, and then centrifuged at 12,500 rpm for 4 minutes. The supernatant was transferred to a vial with a flat bottom glass insert.

Plasma concentrations of metformin were determined using HPLC-MS/MS using an Agilent Technologies (Palo Alto, California) Model 1100 series instrument equipped with a degassing unit, a high pressure binary pump, an autosampler, and a mass spectrometer detector (6410 B; Agilent Technologies), using a method based on that published by Kandhwal et al[15] and Harahap et al.[16] Separations were performed on a Zorbax HILIC Plus Rapid Resolution 4.6 × 100 mm, 3.5 μm column (Agilent Technologies), and eluted with a mobile phase consisting of 2.65 mM acetonitrile and formic acid solution (40%/60% v/v). The eluate was filtered through a 0.45 μm pore size cellulose membrane. The chromatographic separation was performed isocratically at 21°C at a flow rate of 0.8 mL/min.

Tolerability

Tolerability was determined by clinical assessment and monitoring vital signs (eg, blood pressure, heart rate, and body temperature) at baseline, 3 times during the study, and at the end of the periods. Laboratory analyses were also performed before and after the study. In addition, subjects were required to report to the investigators any adverse effects that occurred at any time during the study, including during the washout period.

Pharmacokinetic analysis

The following pharmacokinetic values for each subject and for each treatment were determined: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $T_{1/2}$. AUC_{0-t} was calculated using the linear trapezoidal rule[17] and $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-t} and the extrapolated area under the concentration time curve (C_{last}/elimination rate constant [K_e]). C_{max} and T_{max} were obtained directly from the original data set and $t_{1/2}$ was calculated as ln_2/K_e. K_e was obtained by linear regression from the best-fit slope of the terminal log-linear decay in plasma concentrations versus time profile. All pharmacokinetic analyses were performed using WinNonlin