Bioequivalence and Comparison of Pharmacokinetic Properties of 4-mg Tablet Formulations of Rosiglitazone Hydrochloride and Rosiglitazone Maleate: A Single-Dose, Randomized, Open-Label, Two-Period Crossover Study in Healthy Adult Male Chinese Volunteers

Jia Yu, MS[1]; Ke Ma, BS[1,2]; Jinwen Qi, BS[1]; Ge Jin, MS[1]; Yan Wang, BS[1]; Shungan Fang, BS[1]; and Gonghua Li, BS[1]

[1]Department of Clinical Pharmacology, Zhejiang Provincial People's Hospital, Hangzhou, People's Republic of China; and [2]Department of Pharmacy, Sir Run Run Shaw Hospital Affiliated with School of Medicine, Zhejiang University, Hangzhou, People's Republic of China

ABSTRACT

Background: Rosiglitazone is an insulin-sensitizing oral thiazolidinedione used for treating patients with type 2 diabetes mellitus. There are 9 oral generic and branded formulations of rosiglitazone available in the People's Republic of China (PRC); however, a literature search did not identify any published data concerning the bioavailability of these formulations in the Chinese population.

Objectives: The aims of this study were to compare the pharmacokinetic properties and determine the bioequivalence of 2 formulations of rosiglitazone 4-mg tablets—rosiglitazone hydrochloride (test) and rosiglitazone maleate (reference)—in healthy adult male Chinese volunteers.

Methods: This single-dose, randomized, open-label, 2-period crossover study was conducted at Zhejiang Provincial People's Hospital, Hangzhou, PRC. Healthy adult male Chinese volunteers were randomly assigned to receive a single 4-mg dose of the test or reference formulation, followed by a 7-day washout period and administration of the alternate formulation. The study drugs were administered after a ≥12-hour (overnight) fast. Plasma was analyzed for rosiglitazone concentration using a validated high-performance liquid chromatography method. For analysis of pharmacokinetic properties, including C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, blood samples were drawn before (0 hour; baseline) and at 10, 20, 30, 45, 60, 75, and 90 minutes and 2, 4, 6, 8, 12, and 24 hours after administration. The formulations were to be considered bioequivalent if the logarithm-normal (ln)-transformed ratios of C_{max} and AUC were within the predetermined range of 80% to 125%, as established by the US Food and Drug Administration. Tolerability was assessed using physical examination, including monitoring of vital signs, laboratory testing (hematology, blood biochemistry, hepatic function, renal function, and urinalysis), and questioning subjects about adverse events (AEs).

Results: Twenty subjects were enrolled and completed the study (mean [SD] age, 21.1 [1.4] years; weight, 62.6 [4.6] kg; height, 171 [5] cm; and body mass index, 21.4 [1.3] kg/m^2). No period or sequence effects were detected. The 90% CIs for the ln-transformed ratios of C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were 96.79 to 109.73, 92.14 to 102.93, and 91.64 to 102.60, respectively (all, $P < 0.001$), meeting the predetermined criterion for bioequivalence. No AEs were reported in this study.

Conclusions: In this small study in these healthy adult male Chinese volunteers, a single 4-mg dose of rosiglitazone hydrochloride appeared to be bioequivalent to rosiglitazone maleate, according to the regulatory definition, based on the rate and extent of absorption. Both formulations were well tolerated. (*Clin Ther.* 2008;30: 2272–2279) © 2008 Excerpta Medica Inc.

Key words: rosiglitazone hydrochloride, rosiglitazone maleate, bioequivalence, pharmacokinetics, HPLC, Chinese.

Accepted for publication October 31, 2008
doi:10.1016/j.clinthera.2008.12.011
0149-2918/$32.00

INTRODUCTION

Rosiglitazone (5-[4-[2-[*N*-methyl-*N*-(2-pyridyl)amino]-ethoxy]benzyl]-thiazolidine-2,4-dione), an aminopyridyl thiazolidinedione, is a potent synthetic peroxisome proliferator–activated receptor-γ agonist and effective antidiabetic agent.[1] Rosiglitazone has regulatory approval for the treatment of type 2 diabetes as both monotherapy and in combination with other oral antidiabetic agents.[2,3] In a randomized, double-blind, active-controlled study in 191 patients with type 2 diabetes (fasting plasma glucose, 7.0–15.0 mmol/L; C-peptide, ≥0.27 nmol/L), the most common serious adverse events (AEs) associated with rosiglitazone 8 mg/d use were edema and injury (8.9% and 8.4%, respectively).[4] Recently, patients and providers were reminded by Nissen and Wolski[5] to consider the potential for serious cardiovascular AEs (eg, myocardial infarction, cardiovascular-related death) associated with treatment with rosiglitazone for type 2 diabetes.

The absorption of rosiglitazone is rapid and essentially complete, with a T_{max} of 1 to 2 hours and the absolute bioavailability estimated to be ~99% after oral tablet administration.[6] The C_{max} and AUC increase proportionately with an increase in doses of 0.2 to 20 mg. Rosiglitazone is ~99.8% protein bound, primarily to albumin.[7] Its mean oral V_d is ~17.6 L, approximating the volume of extracellular fluid space. Rosiglitazone is extensively metabolized by 2 major routes, *N*-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. Cytochrome P450 (CYP) 2C8 is predominantly responsible for the drug's metabolism, with CYP2C9 contributing as a minor pathway.[3,6,7] Circulating metabolites, in the form of sulfate and glucuronide, are all considerably less potent than the parent compound and do not appear to contribute to the drug's pharmacologic activity. These metabolites are excreted primarily (~65%) in urine, with the remainder (23%) eliminated in feces.[6] Rosiglitazone has an elimination $t_{1/2}$ of ~3 to 4 hours.[8]

In the People's Republic of China (PRC), the criteria for registration of generic drugs, designated by the State Food and Drug Administration, require that generic drugs be therapeutic equivalents—pharmaceutically equivalent and bioequivalent with the reference formulation manufactured by the designer. Bioequivalence testing was required only in the Chinese population.[9] Bioequivalence or comparative bioavailability of 2 formulations of the same drug comprise equivalence with respect to the rate and extent of absorption. While the AUC generally serves as the primary characteristic of the extent of absorption, the C_{max} and T_{max} reflect the rate of absorption, especially in conventional-release drug formulations.

Although 9 oral generic and branded formulations of rosiglitazone are available in the PRC, a search of PubMed and ScienceDirect in July 2008, with no limit of publication years or languages and using the terms *rosiglitazone, bioequivalence,* and *Chinese*, did not identify any publications concerning the bioequivalence of these formulations in the Chinese population. Thus, the aims of the present study were to compare the pharmacokinetic properties and determine the bioequivalence of the test[10] and reference[11] formulations in a healthy adult male Chinese population.

SUBJECTS AND METHODS

Inclusion and Exclusion Criteria

Healthy adult male volunteers were identified from the database of volunteers at the Department of Clinical Pharmacology, Zhejiang Provincial People's Hospital, Hangzhou, PRC. The database included information on age, sex, weight, height, health, and allergies. Subjects were eligible if they were aged 18 to 40 years; had a body mass index (BMI) between 19 and 24 kg/m^2; were nonsmokers; had normal findings on the clinical history, chest radiography, electrocardiography, and laboratory testing (hematology, blood biochemistry, hepatic function, renal function, and urinalysis); and had negative findings on HIV and hepatitis B and C viral testing.

Subjects were instructed to abstain from using any medications for ≥2 weeks prior to and during the study period. All eligible subjects were informed of the aim and risks of the study by the clinical investigators and provided written informed consent before participating. They were free to withdraw from the study at any time.

Study Design and Procedures

The study had a single-dose, randomized, open-label, 2-period crossover design. The protocol and the informed-consent form were approved by the ethics and research committee at the hospital, and the study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments[12] and the principles of the Good Clinical Practice Guideline.[13]