Comparison of Fasting Bioavailability Among 100-mg Commercial, 100-mg Generic, and 50-mg Chewable Generic Sildenafil Tablets in Healthy Male Mexican Volunteers: A Single-Dose, 3-Period, Crossover Study

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ABSTRACT

Background: Sildenafil citrate (SIL) was the first oral drug registered in Mexico for the treatment of erectile dysfunction. However, succinct pharmacokinetic data are available in the Mexican population.

Objective: The goals of the present work were: (1) to design a specific method to quantify SIL plasma levels by using UPLC-MS/MS; (2) to compare oral SIL bioavailability in Mexican men with pharmacokinetic data in other populations; (3) to fulfill local regulatory requests; and (4) to describe the relative tolerability of a new 50-mg chewable tablet.

Methods: This was a randomized, single-dose, 3-period, 6-sequence crossover study in healthy male volunteers. In each period, subjects received single oral doses of 100 mg of sildenafil (1 commercial [reference*], 1 generic [test 1†], or 2 chewable generic tablets [test 2‡]), with a 4-day washout period between each dose. Serial blood samples were collected for up to 24 hours. SIL was measured in heparinized plasma by using a validated UPLC-MS/MS method. Pharmacokinetic parameters included C_{max}, T_{max}, AUC_{0-24}, and $AUC_{0-\infty}$. Bioequivalence was established if 90% CIs for mean test:reference ratios of log-transformed C_{max} and AUC fell within the range of 0.80 to 1.25. Tolerability was assessed on the basis of a clinical interview with the subject and monitoring of vital signs.

Results: Demographic data showed a homogeneous population. Validation of analytical method proved to be linear within the range of 1 to 1000 ng/mL, with selectivity, accuracy, and precision. 90% CIs for test 1:reference ratios were 86.52 to 113.56, 94.75 to 108.84, and 94.97 to 108.82 for the logarithm parameters C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$, respectively. The 90% CIs for the test 2:reference ratios were 82.14 to 107.24, 98.26 to 112.56, and 99.19 to 113.34 for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$. Regarding relative tolerability, slight cephalea was the most common adverse effect.

Conclusions: The developed analytical method was validated in compliance with local requirements and was useful for sildenafil measurement. This single-dose study under fasting conditions suggests that both test products met the Mexican regulatory criteria for assuming bioequivalence in these healthy, male Mexican volunteers. The clinical data suggest that the chewable tablets were well tolerated by volunteers. Trial registration code number: DIC/09/407/02/020, Research Direction of Hospital General de México, Mexico City, Mexico. (*Clin Ther.* 2012;34:689–698)

Key words: CAS no. 171599-83-0, sildenafil chewable tablet tolerability, sildenafil citrate bioavailability, sildenafil pharmacokinetics, UPLC-MS/MS sildenafil quantification.

INTRODUCTION

Sildenafil citrate (SIL) (CAS no. 171599-83-0) was the first oral drug registered in Mexico (Pfizer, S.A. de

*Trademark: Viagra® (Pfizer, S.A. de C.V., Mexico City, Mexico).
†Trademark: Vimax 100® (Siegfried Rhein, S.A. de C.V., Mexico City, Mexico).
‡Trademark: Vimax 50® (Siegfried Rhein, S.A. de C.V., Mexico City, Mexico).

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Chapter 3

STATISTICAL APPROACHES FOR BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS AND DRUG PRODUCTS

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GENERAL BACKGROUND

Bioequivalence studies play a major role in the development of new drugs and in the marketing of generic formulations; such trials also contribute in to access to low-cost and effective medicines in developing countries. At present, with the loss of patents of novel molecules, the difficulty in designing interchangeability trials has increased.

Several factors contribute to the complexity of bioequivalence studies. Some new drugs are more potent, and their concentrations in biological fluids

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Short communication

Development of an HPLC method for determination of diphenidol in plasma and its application in an oral multi-dose bioequivalence study in a healthy female mexican population

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Abstract

Diphenidol was determined by an HPLC method developed in our laboratory. It was validated and proved to be linear in the 40–400 ng/ml range. Accuracy for quality-control samples for intra and inter day assays ranged from 96.1–98.9% and 98.8–101.4%, respectively. This method was applied to a multi-dose bioequivalence study. No serious side effects were observed in the multi-dose design. Pharmacokinetic parameters (mean ± standard error [S.E.]) of Cavg (ng/ml) and AUC_{tau} (ng h/ml) for reference and test products were 139.54 ± 12.66 versus 148.60 ± 16.51 and 551.07 ± 53.53 versus 588.78 ± 69.02, respectively. Log-transformed values were compared by analysis of variance (ANOVA) followed by the classical 90% confidence interval (CI 90%) test and Schuirmann's test. Confidence limits ranged from 91.48–116.18% for C_{max} and from 91.24–117.65% for AUC_{tau}. These results suggest that the analytical method was linear, precise, and accurate for our purpose, and that both assayed formulations were bioequivalent.

Keywords: Diphenidol pharmacokinetics; Reversed-phase HPLC; Multi-dose clinical trial

1. Introduction

Diphenidol (DPN) [1,1-diphenyl-4-piperidino-1-butanol hydrochloride] (Fig. 1) [CAS No. 3254-89-5] is an non-phenothiazinic antiemetic agent employed for some time as a treatment for vomiting and vertigo, principally in patients with Meniere's disease and labyrinthopathies. DPN has been also used as a prophylactic against nausea and vomiting during surgery, cancer chemotherapy, and radiotherapy. The mechanism by which diphenidol exerts its antiemetic and antivertigo effects is not precisely known. It is thought to diminish vestibular stimulation and depress labyrinthine function. Action on modulating the chemoreceptive trigger zone may also be involved in the effect. DPN also possesses a weak peripheral antimuscarinic action [1,2]. It has been reported to cause serious adverse effects including hallucination and confusion (usually within the third day of therapy or at elevated doses) and occasionally drowsiness, dry mouth, depression, restlessness, headache, and transitory hypotension [1–3].

Following oral administration of DPN, peak concentrations – usually achieved between 1.5 and 3 h and with elimination half-life of approximately 4 h – have been reported [1]. However, no information with regard to its pharmacokinetic profile has been reported, in part due to the fact that determination of DPN in plasma by any method has always been hampered by the problem of stet selectivity and sensitivity due to poor detectability, in that its molar absorption coefficient in UV region is very low. Moreover, the structure does not present either fluorescence or electrochemical properties that can be used for detection by these conventional techniques.

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ORIGINAL RESEARCH

Ultra-fast chromatographic micro-assay for quantification of diphenidol in plasma: application in an oral multi-dose switchability trial

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ABSTRACT: Pharmacokinetics of diphenidol (DPN) is limited due to the lack of analytical methodology. Here, a micro-assay for DPN quantification was developed, by coupling ultra-performance liquid chromatography with tandem mass spectrometry. The procedure involved plasma precipitation and injection of supernatant into UPLC with an Acquity™ C_{18} column. Detection was in positive electrospray, following transitions of *m/z* 310.3 → 292.3 and *m/z* 275.3 → 230.2 for DPN and chlorphenamine (internal standard), respectively. The method was linear with a range of 4–400 ng/mL, and a 2 min run time. This method was applied in a switchability trial, where both formulations of DPN were bioequivalent. Copyright © 2008 John Wiley & Sons, Ltd.

KEYWORDS: CAS 3254-89-5; diphenidol pharmacokinetics; UPLC–mass spectrometry; multi-dose switchability trial

INTRODUCTION

Diphenidol (DPN; 1,1-diphenyl-4-piperidino-1-butanol) is an anti-emetic agent widely used in the Latin American market that is administered orally, rectally and parenterally. It has been proposed that the anti-emetic effect could consist of blunting the chemo-receptor trigger zone in the *area postrema*. Additionally, DPN is prescribed to control vertigo due to its specific effect on the vestibular apparatus (Bryfield *et al.*, 1999). Although new drugs are used at present for the prophylaxis of some forms of chemotherapy-, radiotherapy- and surgery-associated nausea and vomiting, DPN continues to be used in such circumstances because of cost–benefits issues.

Pharmacokinetic data of DPN are scant and limited, due in part to the long use of the molecule and the lack of sensitive methodology. The pharmacokinetics has been previously reported in an oral multi-dose trial in healthy female Mexican volunteers, in which peak plasma concentrations were reported between 0.5 and 1.5 h post-dose, and an elimination half-life *ca* 3 h was calculated during steady state (Hernández *et al.*, 2005). These data were obtained with the unique method previously mentioned: an HPLC technique coupled with UV detection; although this was validated and applied in a bioequivalence trial, it is time-consuming and requires the processing of 2 mL of plasma to reach a moderate sensitivity level (40 ng/mL).

The aim of the present work was to develop a rapid and more sensitive micro-volume assay for specific quantification of DPN in human plasma by coupling ultra-fast liquid chromatography with tandem mass spectrometry, and applying this in a biopharmaceutical switchability trial.

EXPERIMENTAL

Chemical and standard solutions. DPN chloride (purity 99.8%) was from Spectra Lab Products, Inc. (Gardena CA, USA). The chlorphenamine maleate (CLP) used as internal standard (purity 100.6%) was obtained from Retecma S.A. de C.V. (Mexico City, Mexico), while acetonitrile, methanol and acetic acid (HPLC-grade) were purchased from Tecsiquim (Toluca, Mexico). Formic acid (purity 98%) was purchased from Fluka (Hanover, Germany). Water (HPLC-grade) was obtained through a Milli-Q system (Millipore, Bedford MA, USA). The reference product was 25 mg DPN tablets (Vontrol®, SANFER S.A. de C.V., Mexico) and the test product was also 25 mg DPN tablets (Lansenol®, Landsteiner Scientific S.A. de C.V., Mexico).

Stock solutions of DPN (200 µg/mL) and CLP (200 µg/mL) were prepared in methanol–water (1:1 v/v) and protected from light exposure. Working standard solutions of DPN (40–4000 ng/mL), as well as working solution of IS (CLP 100 ng/mL) were prepared in methanol–water (4:1 v/v) and stored at 4°C. For chromatographic purposes, a weak washing solution

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Abbreviations used: CLP, chlorphenamine maleate; DPN, diphenidol; UPLC, ultra-performance liquid chromatography.