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Bioequivalence Study of Metoclopramide Hydrochloride 10 mg Tablets in Healthy Male Volunteers

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Abstract

The aim of this study was to determine if two oral solid formulations of 10 mg of metoclopramide hydrochloride are bioequivalent, after the administration of one dose PO, in fasting conditions, in healthy male subjects.

This study used a single dose, randomized, single-blind, controlled, 2 x 2 cross-over, under fasting conditions, design to compare the 2 products. Subjects received one oral dose of the metoclopramide 10 mg tablet on each treatment period, which were separated by a seven-day wash-out period. Plasma concentrations of unaltered metoclopramide were analyzed by High Performance Liquid Chromatography. Pharmacokinetic parameters were obtained. Schürrmann's unilateral double t test was performed. Null hypotheses indicating bioinequivalence ($p > 0.05$) were rejected. Bioequivalence was determined if the quotient of the parameters of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were between 80 % and 125%, at a power of 80% ($\alpha > 0.08$).

Twenty-five volunteers were enrolled in the study, all were Mexicans with the mean \pm SD age of 27 ± 8 years, height 171 ± 7 cm, weight 70.4 ± 7.3 kg and body mass index: 24.11 ± 2.33 kg/m². The mean $AUC_{0-\infty}$, C_{max} , t_{max} and $t_{1/2}$ were 237.02 ng/h/mL, 36.74 ng/mL, 0.95 h and 5.0 h, respectively, for the test drug and 238.90 ng/h/ml, 37.28 ng/mL, 0.95 h and 4.81 h for the reference product.

This bioavailability comparison in this selected group of healthy male volunteers failed to detect statistically significant differences between the products. These results met the regulatory criteria for assuming bioavailability.

Keywords: Bioequivalent; Metoclopramide; Healthy subjects; Performance liquid chromatography; Bioavailability

Introduction

Metoclopramide (4-amino-5-chloro-2-methoxy-N-(2 diethylaminoethyl) benzamide) is one of the oldest true prokinetic drugs, that is its administration results in coordinated contractions that improve gastrointestinal transit. It is a competitive antagonist of dopamine that accelerates gastric emptying and gastrointestinal transit, inhibiting the relaxation of the upper gastric body, increasing antrum phasic activity, relaxing the superior part of the duodenum and increasing bowel peristalsis. It also increases the basal tone of the gastroesophageal sphincter and avoids gastroesophageal reflux [1-3].

Metoclopramide is readily absorbed from the gastrointestinal tract. Its distribution matches a bi-compartmental model, with low plasma protein binding ($40 \pm 4\%$) and wide tissue diffusion. The absolute oral bioavailability of metoclopramide is $80 \pm 15.5\%$ and the peak plasma concentrations occur approximately 1-2 h after ingesting a single oral dose. Hepatic metabolism of metoclopramide is mediated primarily through the cytochrome P450 CYP2D6 pathway producing glucuronide and sulphate metabolites. The average terminal half-life of metoclopramide is 5-6 h in individuals with normal renal function. Enterohepatic circulation is present [4,5].

Metoclopramide has linear pharmacokinetics over oral doses ranging from 5 to 20 mg [6].

As part of the evidence to support that two solid oral forms of metoclopramide hydrochloride are interchangeable, a bioequivalence

study was performed; in which bioavailability of Carnotprim® tablets, manufactured by Productos Científicos S. A. de C. V., was compared to a reference product: Plasil® tablets, manufactured by Aventis Pharma S. A. de C. V.

In Mexico, the cost of brand-products tend to be higher compared to generic products; it is, therefore, important to demonstrate bioequivalence between generic and the established reference products. Bioequivalence studies are mandatory in Mexico to commercialize a generic product.

Materials and Methods

Subjects

Forty-four healthy male subjects between 18 and 55 years old were recruited for the study. Subjects were identified from Asociación Mexicana para la Investigación Clínica A.C. (AMIC) volunteer

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database and contacted to determine whether they were interested in participating. All subjects provided written informed consent prior to the realization of any study activity or procedure. The informed consent form was reviewed and authorized by an independent Institutional Review Board (Ethics Committee and Research Committee of the Pachuca General Hospital) and also by the National Ministry of Health [7].

Subjects were considered eligible through the realization of a complete clinical evaluation, clinical laboratory studies (complete blood count, blood chemistry, urinalysis, HBV serology and HIV ELISA), chest X-ray and 12-lead electrocardiography. Subjects with clinically significant abnormalities were not considered for the trial. Electrocardiograms were obtained with calibrated devices by trained nurses, and interpreted by a cardiologist. Blood samples for clinical laboratory tests were analyzed at Quest Diagnostics Inc. (Van Nuys, California, USA), a laboratory with Clinical Laboratory Improvement Amendments certification and College of American Pathologists accreditation.

Metoclopramide has notable fluctuations in plasma concentration after an oral dose, only male subjects were eligible to reduce intersubject plasma concentration variability for the study [5] Mexican regulation [8] does not require participation of female subjects or fed studies for this type of research.

Twenty-five healthy male subjects were randomized to study sequences.

Study design

This study was conducted in accordance with the principles established in the Declaration of Helsinki and its reviews, the Good Clinical Practice and national regulatory requirements [8-10].

Study design was an open-label, randomized, controlled, 2 x 2 cross-over, clinical trial; with 2 treatments, 2 study periods and 2 treatment sequence and wash-out period of 7 days between doses. On the first day, subjects were randomized [11] to one of the treatment sequences (Sequence 1: Treatment A followed by treatment B, or Sequence 2: Treatment B followed by treatment A). One dose of the corresponding investigational product (according to the sequence assigned) was administered to each subject for study period.

Investigational products

Two metoclopramide oral formulations were evaluated. Treatment A (test product) was: metoclopramide hydrochloride 10 mg tablets for oral administration, batch: BIO001, expiration date: SEP 2010, manufactured by Productos Científicos S. A. de C. V. (Carnotprim®). Treatment B (reference product) was: metoclopramide hydrochloride 10 mg tablets for oral administration, batch: B7E006, expiration date: OCT 2009, manufactured by Aventis Pharma S. A. de C. V. (Plasil®). The reference product is the product established by the Mexican authority. Mexican regulation provides that the reference product for pharmacokinetic comparisons shall be the first product registered with that active principle in the country. The Ministry of Health publishes and regularly updates this list.

Methods

During study periods, subjects remained in the clinical facilities for at least 12 hours before the dose, and at least 24 hours after it.

During these inpatient periods, subjects remained under standardized conditions regarding physical activity, environmental conditions and diet.

For logistic reasons, subjects were divided into seven groups (six groups of four subjects each and one group with one subject). Activities in each group were performed simultaneously, such as diet, doses and blood sampling. Activities from one group to another were separated by 5 minutes.

The first day of each study period (Day -1) a standard dinner was served 12 hours before dose administration. The second day of each period (Day 0) a standard breakfast, lunch and dinner were served 4, 8, and 12 hours respectively after dose administration. On the last day of each period (Day 1) a free breakfast was served after the last blood sample was obtained. Water consumption was not allowed from 10 hours prior to the dose administration, until 2 hours after it. Investigational product doses were administered PO with 250 mL of water.

During inpatient periods, vital signs (breathing, blood pressure, pulse and heart rate) were measured at admission, in the hour before dose administration, 3.5, 7.0 and 11.0 hours after the dose, and before discharge. Vital signs measurements were performed by qualified nurses, using calibrated instruments and results were analyzed by the study investigators.

On admission to and discharge from each study period, all subjects were given clinical exams to confirm their health status and eligibility for the study. Before the wash-out period, subjects were provided with written instructions for reporting adverse events, concomitant medication, alcohol and tobacco abstention, amongst others. Before admission to the second study period, the investigators questioned the study subjects about compliance with these instructions.

Safety evaluation of investigational products

Adverse events were spontaneously reported by study subjects and actively sought by study investigators, through interviews and physical examinations. Adverse events' treatment association was determined using Naranjo algorithm [12] by the principal investigator.

Subjects received economic compensation for the time spent in the study. The amount was previously reviewed and approved by the Ethics and Research Committees. The subjects were not eligible for participation in any other clinical trials at this site for 60 days after the study termination.

Blood sampling for pharmacokinetic study

Six milliliter blood samples were obtained for the pharmacokinetic characterization. Blood samples were obtained at baseline and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours after the dose of the investigational products.

Blood was drawn using an IV catheter or venipuncture, and collected in heparin sodium tubes (Vacutainer - BD, 1 Becton Drive, Franklin Lakes, NJ). Approximately 0.4 mL of blood was extracted and discarded from the catheter before each sample, and catheters were flushed with 0.08 mL of 1000 IU/mL heparin solution after each sample, to avoid its occlusion.

Blood samples were kept refrigerated (2 to 8°C) for a maximum of one hour before they were centrifuged. Centrifugation was performed

for 15 minutes at 3000 ± 200 rpm (rcf: 1864 g), at 2 to 8°C . The plasma obtained from each sample was transferred to 2 cryotubes (two complete series to be safely transported separately to the analytical facilities), which were immediately stored at $-40 \pm 5^{\circ}\text{C}$ until analysis.

Tolerability

Drug tolerability was clinically assessed by medical personnel who questioned subjects about symptoms of possible adverse event and through evaluation of spontaneous reports from subjects throughout the study period.

Analytical method

Plasma concentrations of unaltered metoclopramide was quantified with a validated High Performance Liquid Chromatography (HPLC) method. The method was validated in selectivity, precision, accuracy, recovery with a limit of detection of 2 ng/mL. Analysis was performed at CAFET – Centro A. F. de Estudios Tecnológicos, S. A., in Mexico D. F., Mexico; which is an analytical laboratory approved by the Mexican Authority.

Methods for Results Evaluation

Evaluations of results were performed via pharmacokinetic analysis, for where a following pharmacokinetic parameters were calculated: C_{\max} , t_{\max} , AUC_{0-t} , $\text{AUC}_{0-\infty}$, Ke and $t_{\frac{1}{2}}$.

Pharmacokinetic variables

Statistical analysis and data processing were executed on WinNonlin® Professional Version 5.0.1., Microsoft® Office Excel® 2007, SAS® version 9.1 (September 2008) and Stat Graphics Plus version 5.0 [13,14].

Pharmacokinetic parameters were calculated by a non-compartmental method. Plasma concentrations versus time were averaged by administered dose and for each sampling time. For each parameter was calculated: Mean, geometric mean, standard deviation, variation quotient, minimum, maximum and number of determinations.

Individual and average pharmacokinetic profiles were characterized for both treatments in arithmetic and semilogarithmic scales.

Statistical analyses

Analysis of variance (ANOVA) was performed to assess the effects of unbalanced sequences, variability in the number of subjects, and extreme inter- and intrasubject variability.

Power analysis indicated that this sample of 25 subjects had adequate size to detect statistically significant differences between the trial and reference products in pharmacokinetic parameters converted to natural logarithms of C_{\max} , AUC_{0-t} , and $\text{AUC}_{0-\infty}$. Schüirmann's unilateral double t test ($p \leq 0.05$) confidence intervals at 90% (80 – 125%) were used, with a power of 80%.

Null hypotheses indicating bioinequivalence ($p > 0.05$) were rejected.

Results

Fourty-four subjects signed informed consent form, 14 were not eligible due to clinically significant abnormalities in diagnostic tests. From the 30 eligible subjects, 25 were enrolled and randomized. All 25

subjects were compliant regarding inclusion and exclusion criteria, and satisfactorily completed the study.

Three adverse events not related to the investigational product were detected during the study. No related adverse event was detected; no serious or unexpected adverse events were detected.

Mean plasmatic concentrations in arithmetic and semilogarithmic scales are shown in Figures 1 and 2.

Mean C_{\max} was 36.4 and 37.28 ng/mL with Carnotprim® and PlasiL®, respectively. This was achieved one hour after the administration of the dose (t_{\max}). Elimination half-life for both products was approximately 5.0 hours.

Bioequivalence of investigational products

Results from pharmacokinetics and bioavailability for both investigational products show that their pharmacokinetic parameters (C_{\max} , AUC and t_{\max}) are similar.

Schüirmann's unilateral double t-test and confidence intervals at 90% conclude that both oral forms of metoclopramide are bioequivalent on C_{\max} , AUC_{0-t} , and $\text{AUC}_{0-\infty}$. Statistical power was higher than 0.8, which indicates that the sample sized allowed adequate pharmacokinetic characterization and comparison of these metoclopramide tablets.

Discussion

Metoclopramide has been in the international market for a long time (more than 30 years), yet despite this fact, an important number of scientific articles about its comparative bioavailability in healthy subjects could not be found.

Metoclopramide shows a great inter-individual variability, which is explained by its great first step hepatic metabolism. Metoclopramide it is still a popular drug in medical practice.

Adverse reactions after prolonged use or with high plasma concentrations is frequent, especially in subjects with concomitant therapy (drug-drug interactions) with drugs metabolized by P450 cytochrome and in patients with liver cirrhosis [15].

Several reports in scientific literature mention pharmacokinetic differences between different populations, in drugs metabolized by P450 cytochrome [16,17] It would very interesting and useful to investigate what would be the case with metoclopramide; its inter-individual variability may increase within different populations, considering the fact that metoclopramide is metabolized mainly by the CYP2D6 [2,18], one of the enzyme families of P450 cytochrome.

The results of the study show that the study formulations are bioequivalent, despite great inter-individual variability in the Mexican population, evidenced by this study (see standard deviation in plasmatic concentration-time curves in Figures 1 and 2).

Metoclopramide has been available in the U.S. since 1979 and its use has increased in the last decade [2] however, in the literature there are few bioequivalence or bioavailability studies with metoclopramide available (none in Mexicans subjects). Drovev et al. [19] conducted a bioequivalence study of metoclopramide in 12 caucasian healthy volunteers (8 female and 4 male). They report a similar value for C_{\max} (35 ± 16.9 ng/mL), AUC_{0-24} (234 ± 188.7 h*ng/mL) and T_{\max} (1.00 ± 0.40) for the reference product, compared with the values that we are

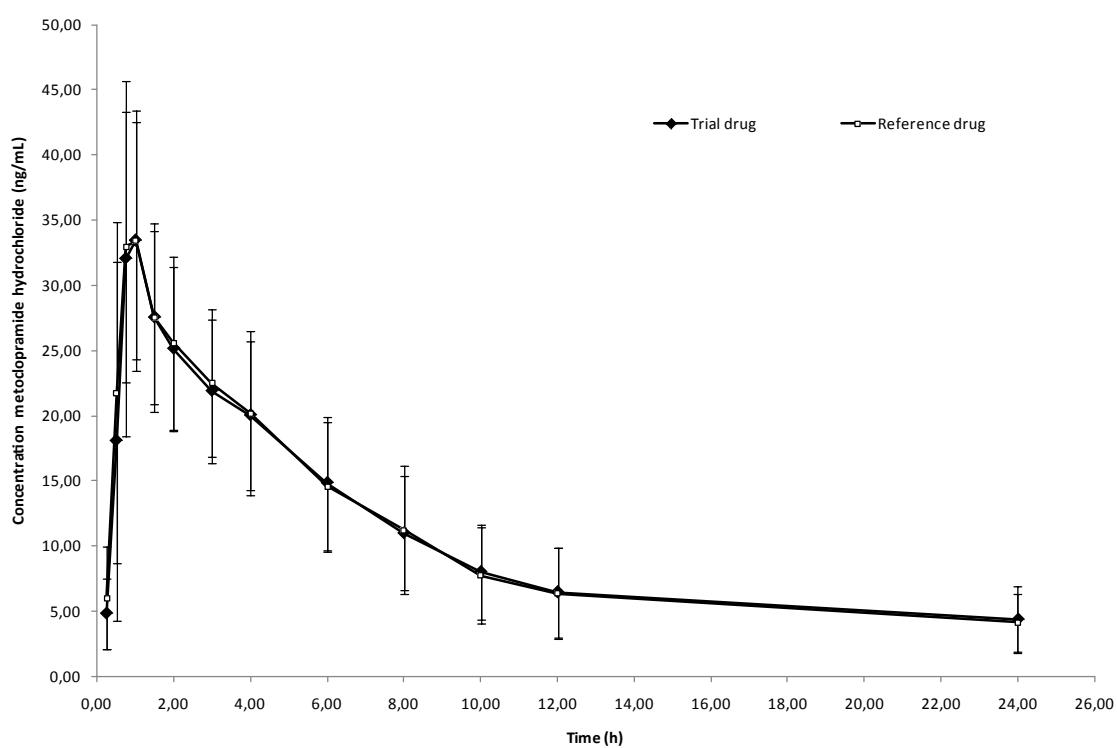


Figure 1: Mean (SD) plasma metoclopramide hydrochloride concentration over time for the test (trademark: Carnotprim®, Laboratorios Productos Científicos S.A de C.V., México City, México) (n=25) and reference (trademark: Plasil®, Aventis Pharma S.A. de C.V.) (n=25). Arithmetic scale.

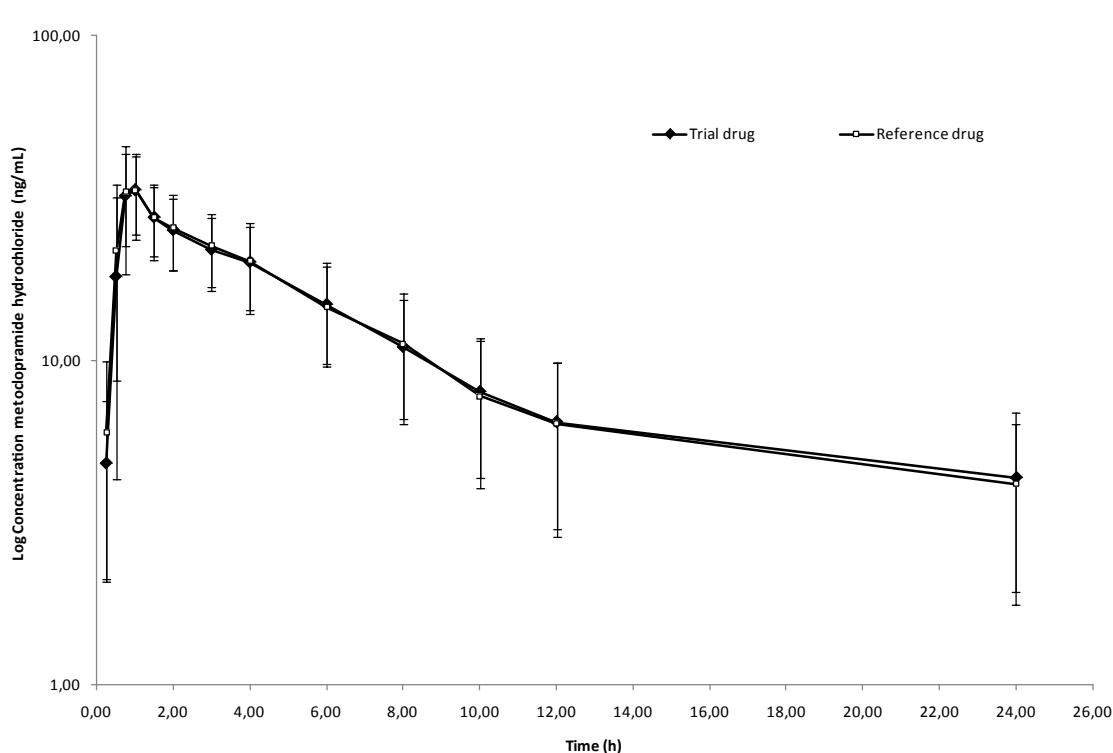


Figure 2: Mean (SD) plasma metoclopramide hydrochloride concentration over time for the test (trademark: Carnotprim®, Laboratorios Productos Científicos S.A de C.V., México City, México) (n=25) and reference (trademark: Plasil®, Aventis Pharma S.A. de C.V.) (n=25). Semilogarithmic scale.

reporting for Mexican healthy male volunteers. It is important to note that this comparison should be taken with caution considering that the samples are not homogeneous.

Conclusions

This single dose study found that the test and reference products

Property	Shüirmann unilateral double-t test $p \leq 0.05$	IC 90 % Ratio of parameters Processed Ln (criteria equivalence 80-125%)	Power ≥ 0.80
In C_{\max}	0.0001 0.0000	90.44 – 105.36	0.9984
In AUC_{0-24h}	0.0000 0.0000	92.41 – 103.12	1.0000
In $AUC_{0-\infty}$	0.0000 0.0000	94.57 – 103.49	1.0000

Table 1: Shüirmann unilateral double-t test, confidence intervals at 90 % (IC 90%) and power of the pharmacokinetic parameters transforms to natural logarithms of 25 subjects.

Property	Test Carnotprim® (n = 25)	Reference Plasil® (n = 25)
C_{\max} (ng/mL)		
Arithmetic mean	36.74 ± 11.61	37.28 ± 9.47
CV (%)	31.61	25.39
Geometric mean	35.04	36.00
Minimum value	19.97	17.83
Maximum value	58.05	53.58
AUC_{0-24h} (h·ng/mL)		
Arithmetic mean	199.29 ± 94.36	203.85 ± 94.69
CV (%)	47.35	46.45
Geometric mean	185.05	189.98
Minimum value	115.52	110.24
Maximum value	531.27	570.68
$AUC_{0-\infty}$ (h·ng/mL)		
Arithmetic mean	237.02 ± 106.89	238.90 ± 106.51
CV (%)	45.10	44.59
Geometric mean	221.51	224.17
Minimum value	131.71	129.15
Maximum value	630.39	665.80
t_{\max} (h)		
Mean	0.95 ± 0.25	0.95 ± 0.38
CV (%)	26.32	40.27
Geometric mean	0.92	0.89
Minimum value	0.5	0.5
Maximum value	1.5	2.0
Ke (1/h)		
Mean	0.151 ± 0.03	0.152 ± 0.03
CV (%)	21.15	21.88
Geometric mean	0.143	0.148
Minimum value	0.078	0.082
Maximum value	0.196	0.252
$t_{1/2}$ (h)		
Arithmetic mean	5.00 ± 1.41	4.81 ± 1.24
CV (%)	28.31	25.80
Geometric mean	4.84	4.68
Minimum value	3.53	2.75
Maximum value	8.88	8.45
%AUC extrapolated		
Arithmetic mean	16.34 ± 4.55	15.16 ± 4.16
CV (%)	27.85	27.46
Geometric mean	15.61	14.56
Minimum value	5.93	6.88
Maximum value	24.47	24.49

Table 2: Pharmacokinetic properties of the test and reference preparations.

Subject No.	Adverse event	Duration	Intensity	Relation to preparation/ preparation
05	Pharyngitis	3 d 12 h	Moderate	Unrelated/test*
08	Rhinitis	7 d	Mild	Unrelated/test*
20	Pharyngitis	9 d	Mild	Unrelated/reference**

*Test: Carnotprim® manufactured by Productos Científicos S.A. de C.V.

**Reference: Plasil® manufactured by Aventis Pharma S.A. de C.V.

Table 3: Adverse events after administration of the reference or test preparations of metoclopramide.

met the regulatory criteria for bioequivalence in these fasting healthy male volunteers.

The study results are reliable and true. The results showed that both study formulations are bioequivalent. None of the study subjects presented serious or unexpected adverse events.

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The sponsor did not participate in study design; collection, analysis, and interpretation of data; or writing of the study report.

Authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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