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Bioavailability of Different Formulations of Metformin Hydrochloride in Healthy Volunteers: a Comparative Study

ORIGINAL

Edilson Martins Rodrigues Neto[1], Lídia Audrey Rocha Valadas Marques[1], Gilmara Holanda da Cunha[2], Andréa Vieira Pontes[1], Patrícia Leal Dantas Lobo[3], Gilberto de Nucci[4], Manoel Odorico de Moraes Filho[1], Maria Elisabete Amaral de Moraes[1]

1 Centre for Drug Research and Development, Federal University of Ceará (UFC), Fortaleza, CE, Brazil.
2 Department of Nursing, Federal University of Ceará (UFC), Fortaleza, CE, Brazil.
3 Dentistry Course, Campus Sobral, Federal University of Ceará (UFC), Sobral, CE, Brazil.
4 Department of Pharmacology, University of São Paulo (UFC), São Paulo, SP, Brazil.

Contact information:

Andréa Vieira Pontes.

Address: R. Cel. Nunes de Melo, 1000, Rodolfo Teófilo. Fortaleza, Brazil. CEP 60430-275.
Tel: +55 85 3366-8033

andreapontes@gmail.com

Abstract

Objective: To assess the bioavailability of a formulation of metformin hydrochloride 850 mg coated tablets as test, compared to a reference product with the same dosage form, in healthy volunteers of both genders.

Method: This clinical trial was designed as randomised, comparative, single-dose, open-label, two-period, two-sequence, crossover study under fasting conditions. 28 healthy volunteers (fourteen men and fourteen women) took part in the study. The 850 mg coated tablets formulations were administered in a single dose orally. Blood samples were obtained prior to dosing and at 30 min, 1, 1:20; 1:40, 2, 2:20, 2:40; 3, 3:20, 3:40 4, 4:30, 5, 6, 8, 12, 16, 24 and 36 hours after drug administration with an one week washout period. Plasmatic concentrations of metformin were measured by specific and validated analytical methods based on high-performance liquid chromatography coupled to mass spectrometry (HPLC/MS). The pharmacokinetics parameter AUC_{0-36h}, $AUC_{0-\infty}$ and C_{max} were tested for bioequivalence after log transformation of data and ratios of Tmax were evaluated non parametrically.

Findings: Data from this study showed that the test and the reference formulation presented similar results, within the acceptance range (80-125%) for $AUC_{0-\infty}$ (area under curve) and C_{max} (maximum serum concentration of the drug) parameters, satisfying the bioequivalence criteria of the Brazilian Health Surveillance Agency and FDA.

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Conclusion: These results indicate that the two formulations of metformin hydrochloride 850 mg coated tablets are bioequivalent, thus, it will be possible to ensure interchangeability between them, which can generate market competition and better access to this treatment.

Keywords
Therapeutic Equivalency; Biological Availability; Clinical Trial; Metformin.

Introduction

Diabetes is a syndrome defined as a condition of heterogeneous metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion and action, or both. This chronic condition increases the risk of developing heart disease, cerebral stroke and microvascular complications. There are frequent demonstrations of blindness, kidney failure and peripheral neuropathy. Currently, Type 2 Diabetes Mellitus (DM2) is a major public health diseases globally, having great impact on the economy of governments and individuals, as to their treatment, in addition to non-pharmacological measures often becomes necessary the use of medications [1].

Metformin is the drug of choice for the treatment of type 2 diabetes and is the most widely prescribed oral hypoglycemic agent due to its low toxicity profile and efficacy. The drug lowers blood glucose levels, especially leading to a decrease in hepatic gluconeogenesis, which leads to an average decrease in insulin levels, and also promotes glucose uptake in muscle. Because of their anti-hyperglycemic properties and normalization of elevated levels of blood glucose, as well as DM2 is also used in polycystic ovary syndrome (PCOS) [2, 3].

Because of its widespread use and socio-economic difficulties of patients, they often choose by the use of generic drugs. Therefore, the reference drugs and generics have in common the same active ingredient, but may differ from each other in relation to excipients and pharmaceutical production process. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulations for generic drug product registration regulations require pharmacokinetic data obtained by comparative bioavailability trials between the formulation reference and test, analyzing the peak plasma concentration parameters (C_{max}), area under the time curve from time 0 to time t (AUC0-t) and extrapolated to infinity ($AUC_{0-\infty}$). For the FDA, the test product should have a confidence interval (CI) of 90% in these three parameters, so that its application is met [2, 4].

Bioavailability studies have several functions, such as assessing the bioequivalence of drugs, evaluation of medicinal products with new active principles, evaluation of new formulations, evaluation of pharmaceutical forms of modified release, evaluation of medicinal products with more than one active ingredient and assessment of change the regimen of a drug [4].

Therefore, we had up to evaluate the bioavailability of a 850mg metformin formulation coated tablet (test formulation) versus a 850mg metformin tablet formulation coated reference in the national market, to analyze the pharmacokinetic parameters of metformin formulations tested healthy fasting volunteers and inter-individual variability in relation to different organic groups, related to the gender.

Methods

Randomised, comparative, open-label, two-period, crossover study in which healthy subjets were given orally after a 8-hour overnight fast, in each distinct

period, a single-dose of the test drug (Metformin 850mg) or the reference product (Glifage®) produced by Merck S.A., according to the randomization plan.

This study was performed at the Clinical Pharmacology Unit (UNIFAC) of the Federal University of Ceara and was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Federal University of Ceará, in Fortaleza, Brazil, with registration number 336.914. All subjects gave their written, informed consent and were free to withdraw from the trial at any time.

Subjects included in the study were considered healthy in the judgment of legally qualified professionals, based on medical history, physical examination and the hematological and biochemical laboratory tests prior to their enrollment. After a period of screening, 28 healthy volunteers (14 females and 14 males) who fulfilled the elegibility criteria were selected.

Inclusion criteria were: both genders, aged 18 to 50 years old, body mass index (BMI) between 18.5 and 28.7 kg/m^2, good health conditions with no clinically significant diseases, ability to understand the nature and purpose of the study, including the risks and adverse effects, intention to cooperate with the researcher and act in accordance with the requirements of the entire clinical trial, which had to be confirmed by signing the informed consent form. Exclusion criteria were: diseases or health problems, addiction habits and pregnancy or breastfeeding.

Volunteers were informed that, with the exception of oral contraceptives, no other drug could not be taken for at least four weeks prior to the study and until after its completion. They were also refrained from ingesting alcohol, caffeine, chocolate, tea or coke containing beverages at least 12 hours before each dosing and until collection of the last blood sample.

The subjects received the drug Metformin Hydrochloride 850 mg test and reference Metformin Hydrochloride 850mg, for oral administration as a single dose, between 7:00 and 8:00 am, the day after confinement in each period. After a minimum of eight hours fasting and evaluation of permanence in the inclusion and exclusion criteria, subjects received one of the formulations under study, having been recorded the absolute real-time medication.

Blood samples of 20 ml were collected for individual control curves patterns 10 ml for time zero through "venous line" heparin introduced in the surface of the volunteer's forearm vein and other samples (7 ml) at the following intervals: 30 min, 1, 1:20; 1:40, 2, 2:20, 2:40; 3, 3:20, 3:40 4, 4:30, 5, 6, 8, 12, 16, 24 and 36 hours after the medication.

The blood samples were centrifuged at 3000 rpm for 12 minutes at 8°C. Immediately after centrifugation, plasma was removed (at least 1,0 ml) and stored in a suitable vial, also identified at the temperature -20°C freezer for storage in a specific biological samples located in the unit. The transport of samples to the analytical unit has occurred according to standard operating procedure for the transport of samples in the current driving period of the study.

Plasma concentrations of metformin were quantified by a specific and validated bioanalytical method based on high-performance liquid chromatography with detection by mass spectrometry (HPLC-MS), and human plasma used as a biological matrix, for quantification pharmacokinetics.

Pharmacokinetic parameters were determined from the plasma concentration-time data. The maximum observed plasma concentration (C_{max}) and the time taken to achieve this maximum level (Tmax) were obtained directly from the curves.The first-order terminal elimination rate constant (Ke) was estimated by linear regression from the points describing the elimination phase on a log-linear plot. The areas under the curve for metformin plasma concentration versus time for 0-36h (AUC_{0-36h}) were calculated by applying the linear trapezoidal method. The extrapolation of this area to infinity

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($AUC_{0-\infty}$) was done by adding the value C36/Ke to the calculated AUC_{0-36} where C_{36} is the metformin plasma concentration at 36h and Ke is the first-order terminal elimination rate constant. The elimination half-life (t1/2) was derived from this rate constant (t1/2 = ln(2)/Ke) where t1/2 is the half-life time, ln(2) is the Neperian logarithm and Ke is the elimination rate constant.

Relative bioavailability between the reference and test formulations was assessed on the basis of maximum plasma concentration of metformin (C_{max}) and area under the plasma concentration versus time curve from time 0 to the last sampling time (AUC_{0-36h}) by calculating the mean ratios and 90% confidence interval (CIs) on log-transformed data. The inclusion of the 90% CIs for the ratios in the 80% to 125% bioequivalence interval, were analyzed using a parametric test (ANOVA). The existence of residual effect was made based on ANOVA sequence tests, using the *P value* obtained based on F_stat of the sequence effect as a parameter (Sequence Hypothesis of Model effects). The variability between the groups (sequence), periods and formulations was evaluated using ANOVA test. The softwares used to calculate the pharmacokinetic parameters (C_{max}) and AUC) and to carry out statistical analysis were WinNonlinTM, version 5.0 (Pharsight, Mountain View, CA); and GraphPad Prim, version 3.02 (Software Inc., San Diego, CA).

Results

The age of the subjects varied between 18 and 39 years old, with an average of 28.5 years old. In assessing the body mass index there was observed a variation of 19,39 to 28,18 kg/m² with an average of 23,7kg/m². Seven volunteers had BMI above 25 are considered overweight, but were included in the study because they have reached the limit of 30 kg/m² BMI. **Table 1** presents means and quantitative variation of these tests in the selection of volunteers **(Table 1)**.

Table 1. Laboratory parameters of the study volunteers (N=28). Fortaleza, CE, 2015.

Clinical analyte		reference value	Average value of the volunteers	The range of variation of the volunteers
Renal function				
Urea	mg/dL	21-53	25.28	16-49
Uric acid		4.0-8.4	4.93	2.5-6.9
Creatinine		0.6-1.2	0.753	0.55-1.08
Liver function				
TGO	U/L	17-59	22.14	15-34
TGP		21-53	19.14	7-37
Alkaline phosphatase		38-126	64.93	39-122
Albumine	g/dL	3.5-5.0	4.58	4.1-5.2*
Total bilirubin	mg/dL	0.1-1.2	0.73	0.22-2.4*
Metabolic evaluation				
Glucose	mg/dL	70-99	82.4	68-98
Total Cholesterol		less than 239	161.25	117-232
Triglycerides		less than 199	82.43	31-177
Blood evaluation				
Red cells	milions/mL	4.2-6.5	4.75	4-5.2
Hemoglobine	g/dL	12-18	13.93	12.1-15.6
Hematocrit	(%)	37-54	41.41	37.1-45.6
Leukocytes	u/mL	3000-11000	7500	4200-12000*
Canes	(%)	1-6	1	1-1
Segmented		40-63	54.93	41-78*
Eosinophils		1-6	2.82	01-07*
Basophils		0-3	0.43	0-1
Lymphocytes		20-45	31.93	14-43
Monocytes		2-10	9.25	05-15*
Platelets	u/mL	130000-400000	271.000	170000-390000

*: Laboratory changes without clinical significance

Tables 2 and **3** show the subjects' pharmacokinetic data accordingly to gender, for the test and reference formulations **(Tables 2** and **3)**. The maxi-

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Table 2. Pharmacokinetic parameters of subjects obtained after the administration of the reference formulation, divided by gender. Fortaleza, CE, 2015.

	C_{max} (ng/mL)	Tmax (h)	t(1/2) (h)	β (1 /h)	ASC (0- 36h) (h*ng/mL)	ASC (0-∞) (h*ng/mL)
Male						
Mean	1,208.15	3.61	4.70	0.16	8,454.01	8,537.08
SD	224.43	0.66	1.87	0.05	1,356.06	1,350.49
Minimum	881.12	2.67	3.13	0.07	5,457.39	5521.35
Maximum	1,570.44	5.00	10.13	0.22	10,204.52	10,241.77
CV(%)	18.58	18.26	39.84	28.54	16.04	15.82
Geometric Mean	1,188.64	3.55	4.44	0.16	8,341.43	8,426.30
Female						
Mean	1,341.82	3.69	6.38	0.12	9,876.52	10,004.48
SD	267.79	0.82	2.77	0.04	2,639.74	2,619.22
Minimum	1,046.29	2.33	3.11	0.05	5,419.43	5,830.07
Maximum	1,844.41	5.00	14.00	0.22	14,808.71	14,949.10
CV(%)	19.96	22.12	43.43	35.66	26.73	26.18
Geometric Mean	1,317.94	3.60	5.93	0.12	9,548.31	9,692.09

Table 3. Pharmacokinetic parameters of subjects obtained after the administration of the test formulation, divided by gender. Fortaleza, CE, 2015. Fortaleza, CE, 2015..

	C_{max} (ng/mL)	Tmax (h)	t(1/2) (h)	β (1/h)	ASC (0- 36h) (h*ng/mL)	ASC (0-∞) (h*ng/mL)
Male						
Mean	1372.57	3.69	5.61	0.13	9857.54	9968.19
SD	212.13	0.80	1.39	0.03	1995.31	2009.72
Minimum	974.07	2.67	4.13	0.08	6728.08	6823.33
Maximum	1817.70	5.00	8.36	0.17	14751.31	14913.65
CV(%)	15.45	21.60	24.68	22.35	20.24	20.16
Geometric Mean	1357.40	3.61	5.47	0.13	9677.14	9787.24
Female						
Mean	1341.82	3.69	6.38	0.12	9876.52	10004.48
SD	267.79	0.82	2.77	0.04	2639.74	2619.22
Minimum	1046.29	2.33	3.11	0.05	5419.43	5830.07
Maximum	1844.41	5.00	14.00	0.22	14808.71	14949.10
CV(%)	19.96	22.12	43.43	35.66	26.73	26.18
Geometric Mean	1317.94	3.60	5.93	0.12	9548.31	9692.09

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mum concentrations (1274.99 and 1302.16 ng/mL for reference and testing respectively) and minimal concentrations (13.42 and 12.8 ng/mL) parameters were remarkably similar, confirming a similar dissolution profile between the formulations and absorption of drugs.

When analyzing the C_{max}, AUC_{0-36h} and $AUC_{0-\infty}$ parameters at **Table 4**, it is noticeable that the variation is within the standard limits (80-125%), considering a confidence interval of 90%. It was also shown that both formulations had similar geometric means for the same parameters.

Table 5 contains the adverse events observed during the study, as well as the measures taken for its treatment, when needed. The events were all of mild or moderate intensity. There were only few

Table 4. Comparative statistical analysis of pharmacokinetic parameters between the two formulations (test and reference). Fortaleza, CE, 2015.

Parameters	Geometric Average ± Standard Deviation		CV_{intra}%	Limits (80-125%)	Power (%)
	Reference	Test		IC (90%)	
C_{max} (ng/mL)	1251.63± 251.82	1280.25 ± 228.49	9.16	98.11-106.64	99.99
$ASC_{(0-36h)}$ (ng*h/mL)	8924.49 ± 2182.91	9162.81 ± 1875.81	9.22	98.45-107.07	
$ASC_{(0-\infty)}$ (ng*h/mL)	9037.06 ± 2177.04	9260.50 ± 1887.28	8.84	98.43-106.68	
T_{max} (h)	3.65 ± 0.73	3.58 ± 0.67	-	-	-
$T_{½}$ (h)	5.54 ± 2.47	5.56 ± 1.68	-	-	-

Table 5. Adverse events observed during the study. Fortaleza, CE, 2015.

Subject	Adverse Event	Intensity	Causality	Duration	Treatment
9	Headache	Low	Not Related	8 hours	Acetaminophen oral, a pill, 750 mg
14	Nausea and vomit	Low	Related	40 minutes	Bromopride, oral, a pill, 10 mg
17	Vomit	Low	Possible	20 minutes	Observation
18	Diarrhea	Low	Possible	1 hour	Observation
	Headache		Remote		
19	Diarrhea	Low	Possible	20 minutes	Observation
	Dor abdominal	Moderate			
20	Nausea and vomit	Low	Not Related	10 minutes	Observation
21	Nausea and vomit	Low	Possible	40 minutes	Bromopride, oral, one pill, 10 mg
22	Headache	Low	Remote	1 hour	Dipyrone, oral, 30 drops, 500 mg/mL
24	Nausea	Low	Possible	1 hour	Observation
	Abdominal pain	Moderate	Possible	15 minutes	
	Diarrhea	Low	Possible		
26	Abdominal pain	Moderate	Possible	20 minutes	Observation
	Diarrhea	Low	Possible		
27	Nausea	Low	Possible	1 hour	Observation
28	Headache	Low	Remote	1 hour	Observation

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situations where the investigator prescribed medication to treat the event, which was limited to the use of antiemetics and analgesics. The reported events were mostly gastrointestinal disturbances (nausea, vomiting and diarrhea), possibly related to the study drug, and headaches, unrelated or remotely related to the drug. Only one event (subject 14) was related to the study drug by the investigator **(Table 5)**.

Discussion

This study supports strong similarity between test and reference formulations in the obtained pharmacokinetic parameters, which are within the specified limits by the regulatory agency. The $AUC_{0-\infty}$ is an important pharmacokinetic parameter that numerically describes the drug bioavailability, with the aim of quantifying the absorbed fraction that reached the systemic circulation and becomes available to exert its pharmacological effect. In this study are found mean values of 9270.78 and 9440.71 hr*ng/mL for the test and reference formulation respectively.

In a study that investigated the pharmacokinetics of metformin hydrochloride tablets 850 mg in six nondiabetic volunteers it was found a mean AUC of 8900 h*ng/mL, similar to the data obtained in this study [5]. Another study found a mean of 15620 h*ng/mL, following the administration of two tablets of the reference product of 500 mg in 12 healthy male volunteers. This elevated concentration was found probably due to the administration of a higher dose of 1000 mg [6].

Regarding the C_{max}, this study found a mean result of 1274.99 and 1299.80 ng/mL for the reference and test formulations respectively, reached at the mean times (T_{max}) of 3.65 and 3.58 hours after the drug administration. The metformin half-lives of the two analysed formulations was of 5.54 (reference) and 5.56 hours (test).

Another study found a mean value of 1.7 mg/l for C_{max}, higher than the two tested formulations in this study [5]. T_{max} had a mean time of 3 hours, which means that concentration peak was reached before both of our studied formulations. The half-life of metformin in this formulation was of 2.7 hours, a value much lower than those obtained in our research. In both studies the formulations were administered under fasting conditions.

A similar result was described in another research, wherein mean values for C_{max} of 1.73 and 1.86 microg/ml were reported, being achieved at 2.6 and 2 hours for the test formulation and reference, respectively. It was also observed C_{max} values higher than in this study, as well as an earlier concentration peak. The half-lives of both formulations were lower than 3.1 hours [7].

After the administration of a 1000mg dose, another study reported mean values for C_{max} of 2.385 g/ml reached at the mean time of 2.72 hours and an elimination half-life of 2.8 hours [6]. A half life of 3.8 hours was found after the administration of Metformin hydrochloride 850 mg tablets to 24 healthy volunteers [8].

Regarding the elevated mean values of the elimination half-life in our tested formulations, it is interesting to note that it may be beneficial, compared with other formulations. Considering that the DM2 is a chronic and sometimes difficult to control disease, a metformin formulation that enables a greater drug residence time in the body can be useful for glucose control in diabetic patients.

The absorption of a drug depends on a complex series of events until it reaches the systemic circulation and is distributed to its site of action. It starts as the pharmaceutical phase, in which the drug is released after the disintegration of the pharmaceutical form allowing its dissolution; During the pharmacokinetics phase, the drug absorption is started by passive transport or by the action of transporters, is distributed in the body, followed by metabolism – majorly hepatic, and degradation in the gastrointestinal tract, either by chemical or microbiological action; and finally the pharmacodynamic phase in

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which the drug acts in its molecular target modulating the physiological response [2].

The differences found between the tested formulations and the cited references can be explained by several factors, including: different formulations, population genetic factors and gender differences. In this study, we found significant differences in the pharmacokinetic parameters between the genders. Female subjects had a mean $C_{max)}$ of 1341.82 and 1372.57 g/mL for the reference and test formulation, respectively, while the male subjects had means of 1208.15 and 1144.67. These differences probably are due to less intense metabolism of women, which generates a reduced drug clearance when compared to man [9].

Data from the $AUC_{0-\infty}$ parameter corroborates this information, showing once again superior pharmacokinetic mean values in women for test and reference formulations (10004.5 e 9938.15 h*ng/mL) than in men (8537.08 e 8828.17 h*ng/mL). Renal excretion is also a very important factor to be considered in differences between genders, since it is known that women have a lower renal elimination rate than men, which can be correlated well with expression of dose-dependent adverse events [10]. These pharmacokinetic differences between genders could be explored, since one of the clinical indications of Metformin is the treatment of polycystic ovary syndrome, a female condition with constant and prolonged treatment [11].

Regarding the adverse events, seventeen were reported during our study, mostly of mild intensity, only three moderate. Eleven events were classified as having a possible relationship with metformin, mainly gastrointestinal reactions. Twelve subjects presented at least one event during the study, only two of them were male. Four subjects had to be medicated for the presented reactions, being prescribed analgesics (paracetamol and dipyrone) and antiemetic agents (bromopride).

Literature references describe that the most common side effects of metformin are gastrointestinal reactions, especially nausea, vomiting, abdominal discomfort, cramps and indigestion. These effects are presented in about 10 to 25% of patients, especially in early treatment. These effects can be reduced if therapy starts with a low dose, gradually increasing, and tend to disappear with continued treatment [2].

Three subjects had headache complaints that can be correlated with abstinence from caffeine and other xanthines [12], which are prohibited substances during the study period, as it could possibly alter the pharmacokinetics of the tested formulations, as they are metabolism inductors of several drugs [13].

Formulations containing metformin were well tolerated, although there was an elevated incidence of adverse events in female subjects. The obtained data are consistent with the literature. It is described that the metabolism and disposition of drugs in women can occur slowly than in man, due to metabolic (hepatic microsomal system) and physiological differences (renal clearance rates). Thus, females have a higher drug concentration peak that can lead to the increased incidence of adverse effects through a dose-dependent mechanism [10].

Conclusion

It is concluded that the test formulation is bioequivalent to the reference formulation for the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$, given the statistical analysis and considering a 90% confidence interval, meeting the requirements set forth for the regulatory agencies ANVISA and FDA (80-125%). The comparative bioavailability trials are important for the confirmation of the efficacy and safety of a new formulation, ensuring the interchangeability between them, generating market competition and improving the population's access to medications.

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