

600 mg Oxcarbazepine Tablets Bioequivalence Study

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Abstract

Bioequivalence studies are evidence of generic drugs quality, demonstrating that the rate and quantity of effective substance absorbed from each of the studied formulations, showed no significant differences. The aim of the pharmacokinetic study of the two formulations, containing 600 mg of Oxcarbazepine, is to analyse bioavailability between the Test Product (Oxicodal[®] from Synthesis Laboratory S.A.S, Colombia) and the Reference Product (Trileptal[®] from Novartis Laboratory) and to affirm the Bioequivalence. Therefore, a study was developed in 24 healthy volunteers; an open, four periods and four randomized sequences, with one dose of 600 mg during fasting and postprandial conditions, and 7-day wash time between each period study. Conducting the study in 4 periods obeys the need to know if there are differences in relation to the presence or not of food during the bioavailability of the formulations studied. The benefits sought in this study are to offer public health a guarantee of quality, safety and inter-changeability of the drugs studied to increase the population's access to generic medicines.

The analytical method used was HPLC chromatography UV detector. The 90% confidence interval for the parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, according to European guidelines and the FDA is within the permitted ranges for the declaration of bioequivalence and compatibility of the Synthesis S.A.S (Colombia) product Oxicodal[®], with the Novartis Laboratories Reference Product Trileptal[®], for both feeding conditions, fasting and postprandial.

Keywords: Bioequivalence; Oxcarbazepine; Anticonvulsant; Pharmacokinetic

Introduction

Oxcarbazepine is indicated as an anticonvulsant in the treatment of partial and generalized conditions [1]. Oxcarbazepine acts by altering the activity of the basic mediators of neuronal excitability, either on the mediators of voltage-dependent ionic channels (sodium channels blockade at brain level), or those controlled by neurotransmitters. It also increases potassium conductance and modulates the calcium channels activity [2]. Oxcarbazepine is a keto-analog of carbamazepine, which is considered a prodrug because of its rapid metabolism to a monohydroxy derivative. Its particular structure helps to reduce the impact on liver metabolism associated with carbamazepine.

This study aims to establish Bioequivalence between two formulations of 600 mg Oxcarbazepine tablets when comparing their bioavailability following a single dose, between the Synthesis S.A.S Test Product (Colombia) and the Novartis Trileptal Reference Product, in both fasting and postprandial feeding conditions.

Materials and Methods

Study of formulations

Test medicament: 600 mg Oxcarbazepine tablets produced and distributed in Colombia by Synthesis S.A.S Laboratories Lot 6A0765.

Reference medicament: Trileptal[®] 600 mg Oxcarbazepine tablets, produced and distributed by Novartis; Lot Z00323.

Subjects

For admission to the study, were taken into account healthy volunteers of both genders, non-smokers, over 18 years of age.

Volunteers underwent medical and laboratory evaluations that included HIV and Hepatitis tests, so that to be diagnosed as healthy before the clinical phase. Women additionally underwent pregnancy test to make sure they were not pregnant. History of alcoholism, drug abuse or pre-existing diseases, were treated as exclusive factors.

Obtaining informed consent

The Protocol and Informed Consent were certified by an independent Ethics Committee, which is authorized by the National Regulatory Authorities, and is governed by the guidelines of the World Conference on Harmonization for Good Clinical Practices for institutions that promotes research in human beings, and by the theory and concept of World Medical Assembly, published in the Declaration of Helsinki [3].

The consent was taken after an individual talk to the volunteers, whose purpose was to explain the study in detail, indicating the variety of drug to be used, the dose, the possible adverse drug reactions, the volume of blood that would be drawn at each stage of study, the dietary restrictions they would face, and answering all questions they had so they could freely decide their participation in the study.

Study design

It was applied as an open, crossed, randomized design, of four periods, four sequences, and a wash time of 7 days during every period. Three days before the beginning of each period, volunteers had to refrain from taking any medication, alcohol and any food or drink containing methylxanthines. This condition was followed during the collection of the samples. All volunteers were randomized and assigned for the sequence of treatment.

Sample taking and drug administration

The process of collection of samples was carried out by a medicine

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Received June 14, 2017; Accepted July 25, 2017; Published August 04, 2017

Citation: Vargas M, Villarraga EA (2017) 600 mg Oxcarbazepine Tablets Bioequivalence Study. J Bioequiv Availab 9: 489-492. doi: [10.4172/jbb.1000350](https://doi.org/10.4172/jbb.1000350)

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doctor and a licensed nurse. Using a Vacutainer®, the blood sample was collected by venepuncture in the upper limb. For periods 1 and 2, volunteers were allowed to fast for 10 hrs, prior to the drug administration, either the Test Product or the Reference Product, which randomly corresponded to each volunteer. The drug dose administered in each period was 600 mg, with 200 mL of water, and the volunteers were allowed to take food only after 4 hrs from the administration of drug [4].

During study periods 3 and 4, in postprandial condition, the volunteers were given standardized diet which was designed by the Nutrition Department of Clínica La Sabana, based on a diet for breakfast that had high lipid content (approximately 50 percent of the total caloric food content) and high in calories (approximately 800 to 1000 kcal), which was programmed in approximately 150 kcal of proteins, 250 kcal of carbohydrates and 500-600 kcal of lipids According to international recommendations [4]. After half an hour, all volunteers were given either the Test Product or the Reference Product, according to randomization. 12 venous blood samples of 8 mL each, were taken at the time intervals of: 0 hr (immediately prior to administration of the drug) 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 and 48 hrs after. Labelling of samples was done for identification and then centrifuged at 3000 rpm for 30 min. Plasma was transferred to a previously labelled tube and frozen at -80°C for further analysis. After 7 days of wash time, the same procedure was repeated, completing periods 2, 3 and 4.

Validation of the analytical method

The bioanalytical method used for the analysis of Oxcarbazepine in plasma, was high performance liquid chromatography with Ultra Violet detection (HPLC-UV).

For the sample preparation, sedimentation was carried out by adding 475 µL of the test sample to a screw cap centrifuge tube that already contained 25 µL of Internal Standard (ISTD) (carbamazepine) (5000 ng/mL). Then this mixture was added with 200 µL of 60% perchloric acid and vortexed for 3 min at 1500 rpm to precipitate the proteins. Finally, it was centrifuged at 5000 rpm for 10 min; then the supernatant was filtered with membrane -0.45 µm and added to the chromatographic system [5,6].

Analyte dissolution was attained by using a Symmetry Shield® C18, 4, 6 mm × 150 mm, 5 µm Column, at a 40°C temperature, employing a HPLC SHIMADZU LC2010, with 215 nm wave length. The detection limit is 28.0 ng/mL, and the quantification limit is 50.0 ng/mL. Both limits are low, which allows making a calibration curve in a broader range towards lower concentrations.

Pharmacokinetic analysis

By using the WinNonlin 5.3 program (Pharsight Corporation, Cary USA) the Pharmacokinetic study was executed, through a non-compartmental analysis. The maximum concentration (C_{max}) and the time to reach it (t_{max}), were calculated from the plasma concentrations readings, as currently approved by FDA [7] and the EMA (European Medicines Agency) [8]. The AUC_{total} was estimated by the addition of the partial AUCs: a) AUC_{0-t} , between zero and the final time point with noticeable concentrations, evaluated by the trapezoidal rule assuring at least 80% of the AUC with the last sample, b) $AUC_{t-\infty}$, estimated as the quotient C/K, where C is the last detectable concentration and K is the slope of the line obtained by linear regression, from the points corresponding to the phase of the drug elimination by linear regression of the natural logarithm of the concentrations [9]. The factors like elimination constant (K_e), half-life ($t_{1/2}$), clearance (Cl), and Mean Residence Time (MRT) were conformed to bioavailability and evaluated after the operation of the non-compartmental analysis.

Statistical analysis

The Analysis of Variance (ANOVA) was applied to estimate possible effects for each variation factor by sequence, period or subjects. For this, the F-test was used with a level of statistical significance of 5% ($\alpha=0.05\%$). Statistical comparison of the logarithmically transformed pharmacokinetic parameters of the two test/reference formulations was performed using the WinNonlin statistical program for the variables C_{max} , AUC and AUC_{all} , that should be within the acceptability range of 80-125%.

Adverse events reporting

The events were registered according to the INVIMA regulations in Disposition N° (1067/08). Since the sample size does not have sufficient statistical power, the cases are reported without statistical estimation.

Results

In this study, 24 healthy volunteers of both genders (50% women and 50% men), of Colombian nationality, who completed the 4 periods, were included in the pharmacokinetic and statistical analysis. Both the analyses were well accepted. Adverse events are presented selecting the in taking condition and the drug studied in relation to the compromised system, according to the OMS recommendation in Table 1.

The averages of the pharmacokinetic parameters, the values of elimination rate, half-life, C_{max} , T_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of each of the studied formulations obtained from all volunteers and in the two feeding conditions (mean ± SD), are presented in Table 2.

		Fasting Condition	
		Reference %	Test %
Nervous System Disorder	Dizziness	4.2	4.2
	Drowsiness	2	0.0
		Post-prandial Condition	
		Reference %	Test%
Nervous System Disorder	Dizziness	20.8	18.7
	Drowsiness	10.4	14.6
	Headache	8.3	2
	Nausea	2	0,0
	Visual Impairment	2	0,0
	Lip Hypoesthesia	0,0	6.2

Table 1: Adverse reactions discriminated by food condition.

The 90% confidence intervals of the logarithmically transformed pharmacokinetic parameters, executed to analyse the bioequivalence between Oxycodal[®], Test Product of Synthesis SAS, and Trileptal[®], Reference Product from Novartis, are shown in Table 3.

Discussion

Oxcarbazepine becomes a therapeutic alternative as an anticonvulsant in the treatment of partial and generalized symptoms. The reduction in treatment costs of neurological pathologies by generic drugs is a desired goal for any health system in the world. Therefore, bioequivalence studies are a good alternative to demonstrate the quality of generic drugs products and allow inferring interchange ability in relation to Reference Products without the need to repeat clinical studies in patients [7,8].

The methodology of this research with healthy volunteers, allowed

determining the formulation effects in the two feeding conditions. The applied analytical method was selective, precise, accurate and robust. The 24 volunteers completed the study and only mild adverse events were reported in both formulations. The washing period was lengthy as compared to the recommended 7 elimination half-lives and guaranteed the absence of the trawling consequence between periods.

This observation aimed to calculate the bioequivalence between two 600 mg Oxcarbazepine formulations. In Graphs 1 and 2, the curves of the mean plasma concentrations vs. time are presented. They are similar for the two feeding conditions. On the other hand, 90% confidence intervals of the proportions test/reference for the evaluated criteria C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, meet the range requested by the FDA and the EMA (Table 4) [7,8].

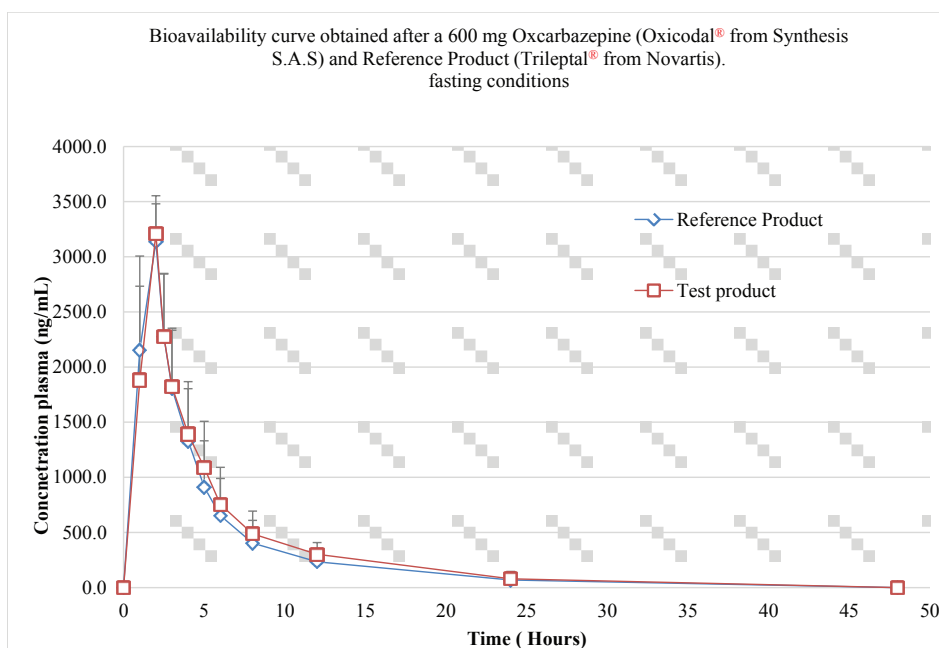
The usage of a single dose layout limited our examination, including healthy women and men. Because the examination was performed on

Fasting Condition						
Treatment	Elimination Rate (1/hr)	Half-life (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
Reference	0,142	6,9	2,0	3135,8	14530,8	14844,5
Test	0,136	6,8	2,0	3209,5	15723,7	15809,6
Fed Condition						
Treatment	Elimination Rate (1/hr)	Half-life (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
Reference	0,193	4,4	2,0	3282,3	13368,7	13164,4
Test	0,175	7,6	2,0	3283,1	14488,2	14464,9

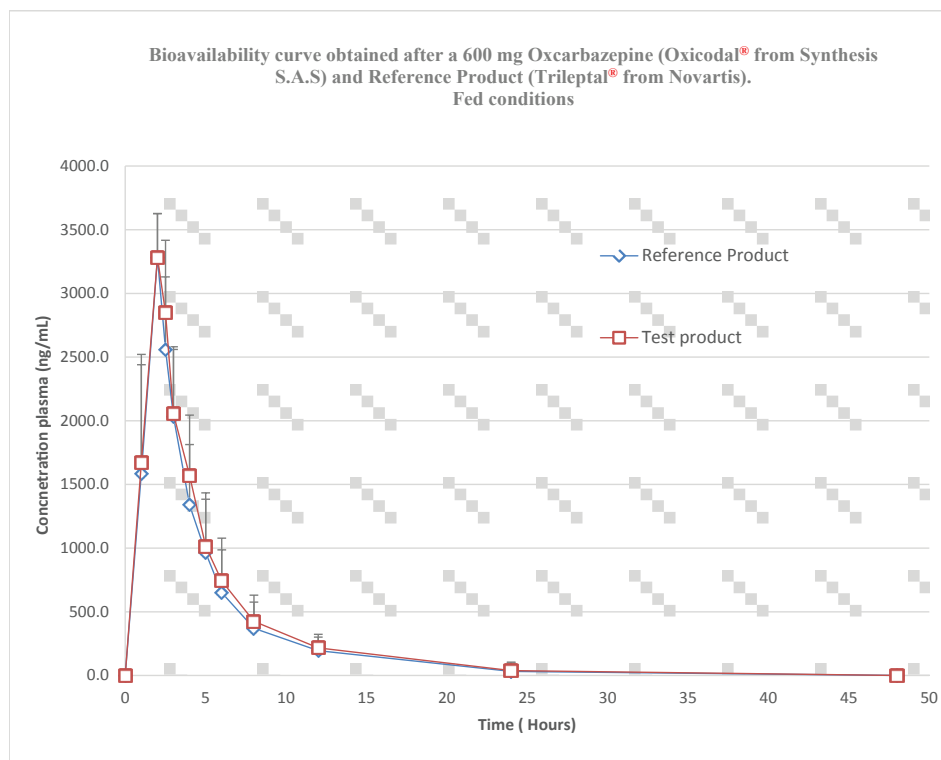
Table 2: Averages of pharmacokinetic parameters discriminated by feeding condition.

Parameter	Units	Ratio %	Standard 90% CI Test/Reference	
			80	125
$\ln(C_{max})$	ng/mL	102,68	99,98	105,46
$\ln(AUC_{all})$	hr*ng/mL	107,19	99,17	115,86
$\ln(AUC_{INF-obs})$	hr*ng/mL	106,01	97,37	115,42

Table 3: Confidence Intervals of 90%, discriminated by feeding condition. Bioequivalence analysis (Confidence Interval 80-125) fasting condition.



Graph 1: Bioavailability curve (Concentration vs. Time) obtained after a 600 mg Oxcarbazepine dose in fasting conditions of Test Product (Oxycodal[®] from Synthesis S.A.S) and Reference Product (Trileptal[®] from Novartis).



Graph 2: Bioavailability curve (Concentration vs. Time) obtained after a 600 mg Oxcarbazepine dose in post prandial condition of Test Product (Oxicodal® from Synthesis S.A.S) and Reference Product (Trileptal® from Novartis).

Parameter	Units	Ratio %	Standard 90% CI (Test/Reference)	
			80	125
Ln(C _{max})	ng/mL	99,77	97,88	101,70
Ln(AUC _{0-t})	hr*ng/mL	107,57	102,00	113,44
Ln(AUC _{0-∞} -obs)	hr*ng/mL	109,47	103,85	115,39

Table 4: Bioequivalence analysis (Confidence Interval 80-125) fed condition.

healthy volunteers, the results are not relative to the patient population or those to having significant medical conditions.

Conclusion

The Oxcarbazepine formulation manufactured by Synthesis S.A.S (Oxicodal®), Test Product, and the one manufactured by Novartis (Trileptal®), Reference Product, have pharmacokinetic parameters that allow declaring bioequivalence between the two formulations, in the two feeding conditions evaluated.

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