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Original Research Article

Bioequivalence of two quinidine gluconate 324mg extended release formulations in healthy Brazilian volunteers under fed conditions: a pilot study

Luciana Ferrara[1]*, Srinivas G.[2]

[1]Clinical Department, Azidus, Brazil
[2]Clinical Department, Azidus, Laboratories Ltd., Chennai, Tamil Nadu, India

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***Correspondence to:**
Dr. Luciana Ferrara,
Email: luciana.ferrara@azidusbrasil.com.br

ABSTRACT

Background: Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity. The present study was aimed at analyzing the bioequivalence of the proposed generic product Quinidine Gluconate 324mg Extended Release Tablets with the marketed product of Sun pharmaceuticals, USA.
Methods: The design was an open, longitudinal, randomized, comparative study of two formulations in single dose of 324 mg, with a 5 days washout in between doses. The study was conducted in 12 healthy adult male and female Brazilian volunteers under fed conditions in Azidus Brasil, Valinhos, Brazil. Blood samples were collected post dose up to 36 hours for pharmacokinetic analysis and safety evaluation was done by assessing the adverse events and laboratory tests. A validated LC-MS/MS method was used to determine the plasma concentrations of Quinidine. Bioequivalence between the products was established by calculating 90% confidence intervals (90% CI) for the ratio of Cmax, AUC0-t and AUC0-∞ values for the proposed generic product and marketed product.
Results: The 90% confidence intervals found for the relation Test/Reference, were Cmax 80.78% to 109.07%, AUC0-t 86.04% to 104.24% and AUC0-∞ 86.25% to 104.71%. There were no clinically relevant changes in the vital parameters and the QT, QTc were not adversely affected and both the drug products were found to be safe and tolerable at the given strength.
Conclusions: According to FDA´s guidelines for Bioequivalence research, the confidence intervals for Cmax, AUC0-t and AUC0-∞ ranged between 80.00-125.00%. The above limits obtained were within the accepted bio-equivalence limits.

Keywords: Bioequivalence, Safety, Quinidine gluconate

INTRODUCTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is the d-isomer of quinine, and its molecular weight is 324.43. Quinidine gluconate is the gluconate salt of quinidine; its chemical name is cinchonan-9-ol, 6'-methoxy-, (9S)-, mono-D-gluconate.[1]

In patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response, quinidine gluconate is indicated as a means of restoring normal sinus rhythm. If this use of quinidine gluconate does not restore sinus rhythm within a reasonable time, then quinidine gluconate should be discontinued.[2]

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4depolarization, shifting the threshold voltage upward toward zero. The result is slowed

conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular defibrillation threshold as well. Quinidine's actions fall into Class Ia in the Vaughn-Williams classification. By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia. In patients with sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in the sinus rate. Like other antiarrhythmic drugs with Class Ia activity, quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes*. In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).[3]

In patients with malaria, quinidine acts primarily as an intra-erythrocytic schizonticide, with little effect upon sporozites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P.* falciparum.[4]

The absolute bioavailability of quinidine from quinidine gluconate is 70 to 80%. Relative to a solution of quinidine sulfate, the bioavailability of quinidine from quinidine gluconate is reported to be 1.03. The less-than-complete bioavailability is thought to be due to first-pass elimination by the liver. Peak serum levels generally appear 3 to 5 hours after dosing; when the drug is taken with food, absorption is increased in both rate (27%) and extent (17%). The rate and extent of absorption of quinidine from quinidine gluconate are not significantly affected by the co-administration of an aluminum-hydroxide antacid. The rate of absorption of quinidine following the ingestion of grapefruit juice may be decreased. The volume of distribution of quinidine is 2 to 3L/kg in healthy young adults, but this may be reduced to as little as 0.5L/kg in patients with congestive heart failure or increased to 3 to 5L/kgin patients with cirrhosis of the liver. At concentrations of 2 to 5mg/L (6.5 to 16.2µmol/L), the fraction of quinidine bound to plasma proteins (mainly to α1-acid glycoprotein and to albumin) is 80 to 88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50 to 70%. Because α1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.[5]

METHODS

Volunteers

A total of 12 healthy adult human male and female Brazilian volunteers between 20 to 45 years (both years inclusive) with BMI of 18.50-30.00Kg/m^2 who were non-smokers and non-alcoholics were enrolled. Healthy volunteers as evaluated by medical history, vitals and general clinical examination, with normal or clinically insignificant laboratory parameters (biochemical, hematological, urinary, serology), Chest X Ray and ECG were selected.

Volunteers with history of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological condition and/or any major surgical procedure in the past three months were excluded from the study. Volunteers with history of alcoholism/ smoking/drug of abuse/ Hypersensitivity, present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 7 days which potentially modify kinetics / dynamics of Quinidine were also excluded from the study. Volunteers who consumed grapefruit and/or its products within 10 days prior to the start of study and subjects who had participated in any other clinical study or who had bled during the last 3 months were excluded from the study.

Informed consent

The protocol and informed consent forms (ICFs) were reviewed and approved by an independent ethics committee prior to study initiation. All the volunteers were informed about the purpose, study nature, procedure, duration, anticipated risks and discomfort of the study in the vernacular language that they understand. A written informed consent was obtained from each one of them prior to study initiation and this clinical trial was conducted in accordance with the Declaration of Helsinki, good Clinical Practice guidelines and national regulatory requirements.[6,7]

Study design

An open label, randomized, balanced, two treatment, two sequence, two period, single dose, cross over, bioequivalence study of Quinidine Gluconate 324mg Extended Release Tablets of a global pharmaceutical company and Quinidine Gluconate 324mg Extended Release Tablets of Sun Pharmaceutical Industries, USA. in healthy, adult, human subjects under fed conditions.

Study subjects received either test or reference in each period as per the randomization schedule. The randomization schedule was generated by using SAS® and each study subject was randomly assigned to one of the dosing sequences. On the day of check in at least 12 hours prior to each dosing, all volunteers were screened for

cocaine, cannabinoids, benzodiazepines, opioids, amphetamines, barbiturates and alcohol.

Drug administration

A single oral dose of test (T) or reference (R) of Quinidine was administered to study subjects in sitting posture at fixed time points with 240±02ml of water, at ambient temperature in each period as per randomization schedule. The subjects were fasted for 10 h prior to the high fat high calorie breakfast and no food was permitted until 4 h after dosing. Drinking water was not permitted 01 hour before dosing and until 01 hour post-dose, at all other times drinking water was permitted *ad libitum*. After administration of the oral dose, a mouth check was performed under supervision of quality control personnel to assess the compliance to this procedure. After dosing, the volunteers were to remain in supine posture for first 12 h. The subjects received standard food approximately at 04.00, 08.00 and 12.00 hours post-dose with time flexibility of +15 minutes. Wash out period of 5 days was given between two dosing periods.

Blood sampling

A total of 22 blood samples (5ml each) were collected using pre-labeled vacutainers containing K3EDTA anticoagulant at -00.00 (hours) (Pre-dose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.50, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours post dose (Total 22 samples). All the samples were collected in the clinic. First 19 samples were collected in the clinic through an indwelling cannula placed in a forearm / arm and remaining samples were collected through direct venous puncture.

Blood samples collected during the study were centrifuged at 4000rpm for 10 minutes at 4±2°C. Plasma was separated into single aliquot and stored at about -20°C or colder for analysis.

Analytical method

A validated LC-MS/MS bio-analytical method was used for estimation of Quinidine in plasma. Bioanalytical method validation was done as per FDA's Bioanalytical Method Validation guidance on Specificity, Sensitivity, Precision and Accuracy, Stability, Recovery and Dilution Integrity.

The method involved protein precipitation. Quinidine D3 was used as internal standard for the estimation. The LC-MS-MS consisted of liquid chromatographic system coupled with a triple quadrupole mass spectrometer (GOTQS) Waters corporation USA, equipped with ESI source for the ionization (positive ionization mode). Integration was done using Mass Lynx software. Detection was done by multi reaction monitoring (MRM) mode, using the positive mode.

The calibration curve range used for estimation of Quinidine is within concentration range of 10.560 to 2082.915ng/ml.

Pharmacokinetic parameters and statistical analysis

The Pharmacokinetic parameters (Cmax, AUC_{0-t} and $AUC_{0-\infty}$ T_{max}, $T_{½}$, K_{el} and AUC_%Extrap_Obs) were calculated using Non compartmental Model of Phoenix® WinNonlin v 7.0.

Statistical analysis was performed on the Ln-transformed pharmacokinetic parameters using SAS® v 9.4. The analysis included data from subjects who completed both the periods of the study.

The log-transformed pharmacokinetic parameters (Cmax, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using ANOVA Model with the main effects of treatment, period, subjects nested within sequence and sequence as fixed effects. The log transformed primary PK parameters (Cmax, AUC_{0-t} and $AUC_{0-\infty}$.) were subjected to ratio analysis. The Test / Reference ratio was calculated for log transformed primary PK parameters.

To establish bioequivalence of the test product with that of reference product, 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the Ln transformed PK parameters (Cmax, AUC_{0-t} and $AUC_{0-\infty}$) must fall between 80.00% to 125.00%.

Safety analysis

All the volunteers were monitored throughout the study for any changes in the health conditions. The QT and QTc were continuously monitored after dosing to observe any changes in the QT and QTc of volunteers. Vital parameters such as Pulse rate, Oral temperature and Blood pressure were monitored at prefixed time intervals. As a part of safety assessment, all the subjects were enquired about their well-being and discomforts (if any). There was only one adverse event reported with marketed product throughout the course of the study. There were no clinically relevant changes observed in QTc throughout the study.

RESULTS

Pharmacokinetics and statistics

In the present study, 12 healthy male and female volunteers (06 males and 06 females) who completed both the periods were included in the pharmacokinetic analysis.

The plasma concentration vs. time curve of test and reference in fed conditions is presented in Figure 1. The Geometric mean ratios, 90% CI, power and intra-subject coefficient of variation of test and references for Ln transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for are presented in Table 1.

Table 1: The Geometric mean ratios, 90% CIs, power and intra subject coefficient of variation of test and reference for Ln transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Quinidine 324mg is presented.

Dependent	T/R ratio	Reference geometric mean	Test geometric mean	CI_90_Lower	CI_90_Upper	Intra subject %CV	Power
Ln(Cmax)	93.86%	950.2850	891.9621	80.78%	109.07%	20.50%	0.8006
Ln(AUC_{0-t})	94.70%	10025.9530	9494.7038	86.04%	104.24%	13.02%	0.9814
Ln($AUC_{0-\infty}$)	95.03%	10473.2400	9952.8477	86.25%	104.71%	13.16%	0.9799

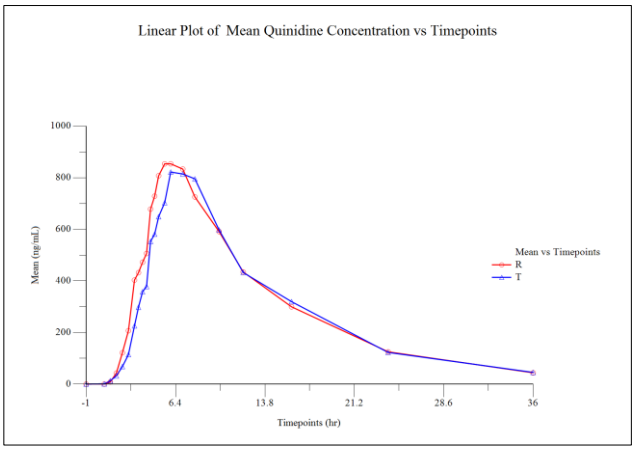

Figure 1: Bioavailability curve (Mean plasma concentration vs. Time) of test and reference in fed conditions.

Safety

There was 01 adverse event which was reported during the conduct of study. Among the 12 volunteers who completed the study, only one subject administered with the reference product had fever and was ascertained to be possibly related to the study drug.

There were no clinically relevant changes in the vital parameters and the QT, QTc were not adversely affected by the test and reference drugs in any of the subjects. The post study ECGs taken at the end of the study did not show any abnormalities. Both the drug products were found to be safe and tolerable at the given strength.

DISCUSSION

Bioequivalence studies allow for the interchangeability of generic products versus reference products without repeating clinical trials in patients.[8] To establish therapeutic equivalence, the two drug products should contain the same active ingredient(s), with the same dosage form, route of administration and should be identical in strength or concentration. Two drug products (of the same active ingredient) are considered bioequivalent when the rate and extent of biologic absorption of the active ingredients is essentially similar when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions.[9] The extent of absorption is indicated by the Area under the curve (AUC), whereas C_{max} and T_{max} are considered estimators of the rate of absorption. According to U.S. Food and Drug Administration bioequivalence between two drug products can only be assumed when the characteristic parameters of bioavailability show no more than a defined difference, which depends on the nature of the drug, the subject population, and the clinical end point.[10]

In this study, the pharmacokinetics of two Quinidine formulations were evaluated and compared in healthy male volunteers. The rate (Cmax) and extent (AUC) of absorption of the test formulation was not statistically significantly different from the rate and extent of absorption of the reference formulation.

CONCLUSION

In this study, based on the statistical results, it can be concluded that the test and reference products met the bioequivalence limits set by regulatory agencies for bioequivalence. The large intra subject variability of 20.50% indicates the drug is moderately variable.

Though the main objective of the study is to establish the bioequivalence, the safety of the subjects was also considered as a parameter to determine the interchangeability between test and reference products. In this study, the test and reference products were well tolerated throughout the study period and were found to be safe in healthy volunteers.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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