

Impact Factor 6.1



Journal of Cyber Security

ISSN:2096-1146

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Comparative Bioavailability of Clopidogrel Formulation in Healthy Volunteers After a Single Dose Administration

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The study was performed to compare the bioavailability of two Clopidogrel 75 mg tablet formulation (Plofixine from Asia- Syria as test formulation and Plavix from Sanofi-aventis-France, as reference formulation) in 6 male healthy volunteers. The study was conducted open with randomized two period crossover design and one week wash out period. Plasma samples were obtained over a 3hour interval. The carboxylic acid of Clopidogrel, major metabolite of Clopidogrel, was analyzed by LC-MS-MS, in the presence of clopidogrel-D4-carboxylic acid as internal standard. With plasma concentration vs. time curves, data obtained from this metabolite, the following pharmacokinetics parameters were obtained: Cmax, AUC0-t and Tmax. The mean AUC0-t and Cmax following oral administration of Plofixine and Plavix tablet, were 6119.84 , 5585.81 for AUC0-t and 4185.67, 3913.17ng/ml for Cmax respectively. The average time required to attain maximum plasma concentration (Tmax) was 1.1and 0.997 hours for Plofixine and Plavix respectively, indicating that, the mean values were found to be similar for both the reference and test product and the value was 1.0 h. The 90% confidence intervals were 95-125% for AUC0-t, and 85-133% for Cmax. According to the 90% confidence intervals for the AUC0-t and Cmax proposed by US Food and Drug Administration, it was concluded that Plofixine 75 mg tablet was bioequivalent to Plavix 75 mg tablet for the extent of absorption, and not bioequivalent for the rate of absorption. According to some regional regulation such as GCC regulations on Drug Bioequivalence, the two products could be considered bioequivalent in the rate and extent of absorption too. The method of analysis which used was simple and suitable to evaluate the bioequivalence and clinical pharmacokinetic of clopidogrel.

Keywords: Therapeutic equivalency, Biological availability, Chromatography, Bioequivalence, Clopidogrel

INTRODUCTION

The increasing number of Clopidogrel containing products available in the Yemeni market raises questions of therapeutic equivalence. For that reason, Clopidogrel, the potent antiplatelet and antithrombotic drug was selected to assess its quality with their counter part of different sources , because it is widely used as a single compound for the reduction of atherosclerotic events. Clopidogrel hydrogen sulfate, methyl (+)-(S)-a-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-

acetatehydrogensulfate, is a novel thienopyridine derivative that irreversibly blocks adenosine diphosphate (ADP) and is important in platelet aggregation, the cross-linking of platelets by fibrin. Clopidogrel is chemically related to Ticlopidine with superior side effects profile and dosing requirements [Majerus and Tollesen 2006, Mills et al. 1992, PLAVIXTM RxMed].

Pharmacokinetics of Clopidogrel

The drug is rapidly but incompletely absorbed after oral administration and extensively metabolized to an active

metabolite. The parent drug or its active metabolite remains undetectable in plasma. The major circulating compound, however, is an inactive carboxylic derivative, which is used to document the pharmacokinetic profile of clopidogrel [Herbert et al. 1993].

The pharmacokinetic parameters of clopidogrel have been characterized by this inactive carboxylic acid metabolite in human plasma. An inactive carboxylic derivative represents 85% of circulating metabolites in human plasma [Rao et al. 2003]. The elimination half life of this compound is 8 hours [Kim et al. 2008, Ksycinska et al. 2006, McEwen et al. 1996]. The platelet inhibition with clopidogrel lasts the lifespan of the platelet (7–10 days) [Hongo et al. 2002, McEwen et al. 1996, Vilahur et al. 2007].

Clopidogrel is inactive in vitro and hepatic biotransformation via the cytochrome P450 pathway, is essential for its in vivo antiplatelet activity [Kim et al. 2008]. The active metabolite, 5-thiol compound, is formed by the oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active metabolite is highly labile and remains undetected in plasma [

Clopidogrel and its metabolite bind reversibly to human plasma proteins (94–98%) and are excreted in both urine and feces with an elimination half-life of eight hours [Kulkarni and Clopidogrel 2000].

Pharmacodynamics of Clopidogrel

Clopidogrel is a potent, non-competitive inhibitor of adenosine diphosphate (ADP) induced platelet aggregation, irreversibly inhibiting the binding of ADP to its platelet membrane receptors [Escolar G and Heras 2001]. The inhibition is specific and does not significantly affect cyclooxygenase or arachidonic acid metabolism [Schrör 1993, Weber et al. 1999].

Indication of Clopidogrel

Clopidogrel is the drug of choice to prevent thrombosis after coronary artery stenting [CAPRIE Steering Committee 1996, Gurbel et al. 2002].

Quantification of carboxylic acid metabolite would be an indirect approach for studying the pharmacokinetics of clopidogrel [Lagorce et al. 1998, McEwen et al. 1996, Singh et al. 2005, Souri et al. 2006].

The objective of this study was, to compare the bioavailability of two oral formulations of 75 mg Clopidogrel tablet, Ploflexine, from Asia Pharma- Syria as a test formulation and Plavix from Sanofi-aventis as reference formulation, by determination of clopidogrel carboxylic acid in human plasma in healthy volunteers.

METHODS

Study protocol

This research were carried out in accordance with conditions stipulated by International clinical research guidelines and the principles enunciated in the Declaration of Helsinki resolved in Helsinki in 1964 and amended in Scotland, 2000; note added in Washington, 2002, note added in Tokyo 2004 also an updated was done in Seoul 2008 and the ICH harmonized tripartite guideline regarding Good Clinical Practice (GCP) adopted by the European Agency for the Evaluation of Medicinal Products. In addition, all local regulatory requirements were adhered to, in particular those which afford greater protection to the safety of the study participants. Informed consent was obtained from participants prior to study commencement. The clinical part of the study was conducted at Daralhayat hospital, Sana'a, Yemen, and the pharmaceutical analysis was carried out at International Pharmaceutical Research Center (IPRC), Amman, Jordan.

Subjects

Six healthy male volunteers who were between the ages of 21 and 34 years old, who had heights between 150.0 cm and 190.0 cm and who weighed between 53 kg and 83 kg and within 15% of their ideal body weight were enrolled in the study. Subjects were judged eligible for enrolment in this study if they were in compliance with all the inclusion and exclusion criteria described in the protocol.

All the subjects provided written informed consent to participate after explaining the nature and purpose of the study. The study protocol was approved by the ethical committee of Yemen University according with the ethical principles described in the Declaration of Helsinki, guidelines for International Conference on Harmonization-Good clinical practices (ICH-GCP).

All volunteers were healthy as assessed by physical examination, ECG, and the following laboratory tests: blood glucose, urea, creatinine, AST, ALT, alkaline phosphatase, Gamma GT, total bilirubin, albumin and total protein, triglycerides, total cholesterol, hemoglobin, hematocrit, total and differential white cell counts and routine urine. All subjects were negative for HIV, HBV (except for serological scare) and HCV.

Drug products

The test formulation employed was Ploflexine 75 mg tablet, from Asia pharma. Co. Syria (lot number 10297) and the reference formulation was Plavix 75 mg tablet

, from Sanofi- aventis(lot number 2464).

Study Design

The study was performed to compare the bioavailability of two Clopidogrel 75 mg tablet formulation (Plofixine from Asia pharma. Co. Syria as test formulation and Plavix from Sanofi-aventis, as reference formulation) under fasting conditions. Formulation was tested for bioequivalence for the first time. The study was conducted in an open randomized two period crossover balanced design with a one week wash out period between the doses.

In the evening before administration on Study Day 1 of Study Period I and II, subjects were admitted to the Clinical Site. A standardized dinner was served at least 10 hours before study. Following the overnight fast of at least 10 hours (in Period I and II), subjects were administered a single dose (75mg) of the test or the reference product with 240 ml of water. During each study period the subject were allowed to consume water as desired except for 1 hour before and after the dose but xanthine containing drinks were avoided. The subjects will remain ambulatory or seated upright for the first five hours following study drug administration and were not engaged in strenuous activity at any time during the housing period. However, should medical events occur at any time, the subjects may be placed in an appropriate position or allowed to lie down in a supine position. Systolic and Diastolic arterial blood pressure, heart rate and temperature were recorded just before and hourly after drug administration. Blood samples (5 mL) from a suitable antecubital vein were collected in heparinized tubes before dosing (0.00 hour)and at the following times after the dose 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5 and 3 hours.

Drug analysis

Blood samples were collected at the times specified under the sampling schedule, using a short intravenous catheter. The blood samples (5ml) were collected into 5ml heparinized tubes and centrifuged immediately at 4000 r.p.m for 5 minutes at room temperature. The separated plasma samples were transferred directly into plain plastic tubes. These samples were immediately frozen and stored in a freezer at a temperature of -20°C until analysis. Plasma concentrations of carboxylic acid of Clopidogrel, the major metabolite of Clopidogrel, were determined by an HPLC coupled with tandem mass spectrometry (LC/MS/MS), using clopidogrel-d4-carboxylic acid as internal standard (IS). This apparatus consisted of Agilent 1100 series degasser, Agilent 1100 Binary pump, Agilen1100 series auto sampler and Agilent 1100 series column oven (Agilent, Germany),

API4000LC/MS/MS systems (mass detectors), Symmetry C18 3.5 μ m 4.6x75 mm (Waters,USA), and Micromass QuattroLC triple-quadrupole mass spectrometer. The analyte was extracted from 200 μ l of plasma by adding 30 μ l of concentrated formic acid and vortex for about 30 seconds, then 6 ml of 20% n-hexane: 80% diethyl ether were added and mixed for about 60 seconds, and centrifuged for 5 minutes at 4000 r.p.m. The organic layer was evaporated in water bath at 40 °C under gentle stream of nitrogen gas. The residue was reconstituted with 200 μ l of mobile phase and 25 μ l injected into the system. The validated method shows a Lower limit of quantification of 25ng/mL and linearity > 0, 999. The mobile phase used was a mixture of Methanol,de-ionized water and formic acid (75% : 25%: 0.1%).The chromatographic run time lasted 5.0 minutes with flow rate of 0.5 mL/min, at ambient temperature.

Pharmacokinetic analysis and statistical analysis

The maximum observed plasma concentration (Cmax) and the time taken to achieve this concentration (Tmax) were obtained directly from the curves. The AUC from 0 to 3 hours were calculated by applying the analyst software (Applied Biosystems, MDS, SCIEX, Canada) The comparative concentration level between both formulations was assessed by calculating individual AUC0-t, Cmax and 90%confidence intervals (CI).

RESULTS

Tolerability analysis

Clopidogrel was well tolerated at the administered dose. No adverse effects were either reported or observed.

Pharmacokinetic and statistical analysis

The mean plasma concentration versus time profile of the two drugs shown in Figure 1. The mean pharmacokinetic parameters of Clopidogrel carboxylic acid of test and reference are shown in Table 1.

The mean values of maximum plasma concentration (Cmax) following the oral administration of Plofixine and Plavix tablet, were 4185.667ng/ml (\pm 877.7 SD) and 3913.17 ng/ml(\pm 621.29 SD) respectively. The average time required to attain maximum plasma concentration (Tmax) was 1.1and 0.997 hours for Plofixine and plavix respectively. The mean values for AUC0-3 were found to be 6119.84 (\pm 1168.83) and 5585.81(\pm 755.36) ng.h/ml for Plofixine and Plavix respectively.

Acceptance Ranges

The united States Food and Drug Administration (USFDA)[3] considers two products bioequivalent if the

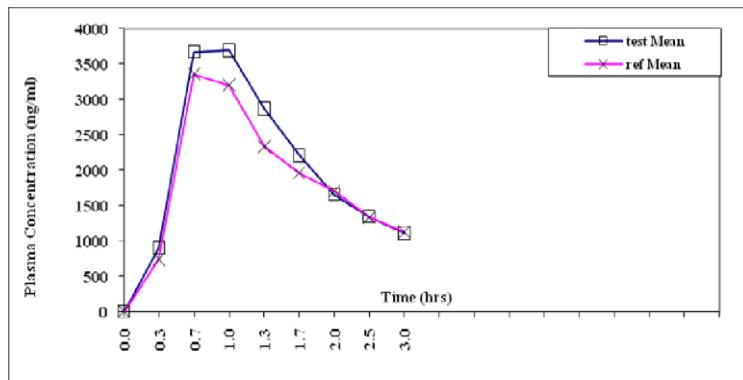


Figure 1. Mean Clopidogrel carboxylic acid plasma Concentration- Time profile after the administration of both drugs, tested and reference (mean of 6 subject)

Table1: The pharmacokinetic parameters for Clopidogrel carboxylic acid (AUC, Cmax and tmax) , following a single oral dose of test and reference drug (n=6, mean \pm SD).

Treatment	AUC_{0-t} ngxh/ml	C_{max} ng/ml	T_{max} h
Tested (SD)	6119.84 (1168.835)	4185.667 (877.733)	1.108 (0.343)
Reference (SD)	5585.812 (755.360)	3913.167 (621.296)	0.996 (0.518)
*Ratio 90% CI)	95-125%	85-133%	

AUC_{0-t} Area under the plasma concentration-time curve from time zero to t hours
C_{max} Maximum plasma concentration
T_{max} Time for maximum concentration
SD Standard deviation
CI Confidence intervals

*Log-transformed values

90% CI of the relative mean Cmax and AUC of the test to reference within 80% - 125% in the fasting state.

According to European Medicines Agency (EMEA) [Committee for Property Medicinal Products 2001], two medicinal products are bioequivalent if the 90% confidence intervals of the transformed natural log ratios, between the two preparations, of Cmax and AUC lie in the range 0.80-1.25.

According to Gulf Cooperation Countries (GCC) regulation[6], regarding AUC, the 90% CI should generally be within 80% -125% (when log-transformed data are used). For drugs with a particularly narrow therapeutic range, the AUC acceptance range may need to be smaller, and this should be justified clinically.

Cmax does not characterize the rate of absorption particularly well in many cases and there is no consensus at present time on any other concentration-based parameter, which might be more suitable. The acceptance range for Cmax may be wider than AUC. The recommended range is between 70% - 143% (when log-

transformed data are used). The range used should be justified taking into account safety and efficacy.

DISCUSSION

Determination of clopidogrel carboxylic acid would be an indirect approach to monitor the therapeutic drug in clopidogrel-treated patients and to characterize the anti platelet action of clopidogrel.

Several analytical methods have been reported for determination of Clopidogrel carboxylic acid in biological fluids[Lagorce et al. 1998, Mitakos and Panderi 2004 , Singh et al. 2005, Souri et al. 2006]. LC/MS/MS methods [Majerus and Tollesen 2006, Nirogi et al. 2006, Robinson et al. 2006, Shin and Yoo 2007]have been reported for the determination of clopidogrel in plasma Taubert et al., [29] reported an LC/MS/MS method for the simultaneous quantification of clopidogrel and its carboxylic acid in human plasma, in which no internal

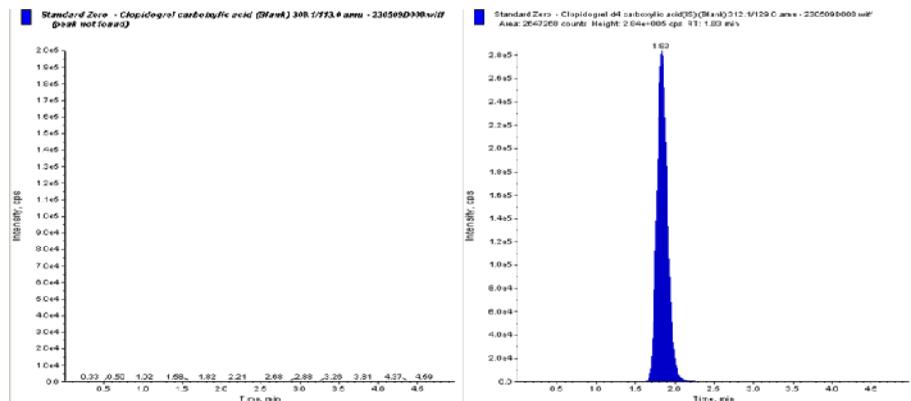


Figure 2. LC/MS/MS chromatogram showing a standard zero sample for Clopidogrel carboxylic acid containing internal standard (Clopidogrel-d4-carboxylic acid) 500.00 ng/ml.

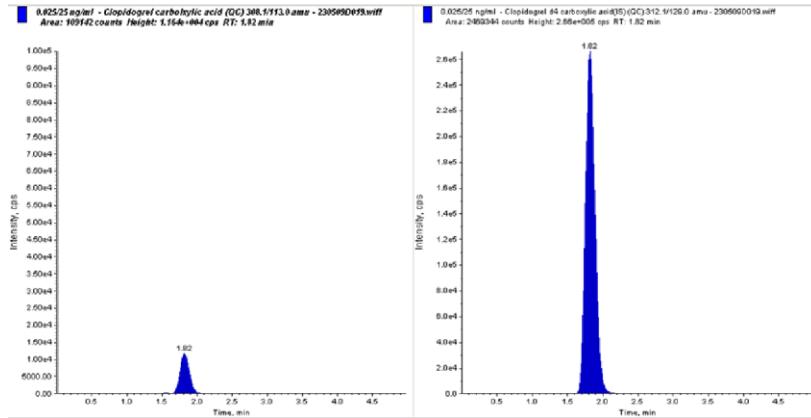


Figure 3. LC/MS/MS chromatogram showing human plasma sample Clopidogrel carboxylic acid (LLOQ sample) containing 25 ng/ml Clopidogrel carboxylic acid and 500.00 ng/ml internal standard (Clopidogrel-d4-carboxylic acid).

standards were used. Recently, Mani et al., [Mani et al. 2006] and Abib E et al., [Abib et al. 2010] developed a LC/MS/MS method for the simultaneous determination of clopidogrel carboxylic acid in human plasma, with the LLOQ of 25 and 10 ng/mL respectively, but the employed procedure of solid-phase extraction (SPE) was complicated. In order to monitor the therapeutic drug in clopidogrel-treated patients, a more sensitive and simple method was required. In the present study, a sensitive LC/MS/MS method is reported for the simultaneous determination of clopidogrel carboxylic acid in human plasma. The internal standards were Clopidogrel-d4-carboxylic acid, and the LLOQ values of 25ng/mL were found to be reproducible. The major advantages of the method are simplicity, selectivity and sensitivity (LLOQ 25 ng/ml). The chromatographic run time was 4.0 minutes which allows determination of the analyte more precisely.

Representative chromatograms are shown in Figures 3,4. All samples were found to show no interference at the retention times of the analytes. The method has been successfully applied to the therapeutic drug monitoring of clopidogrel in clopidogrel-treated patients.

In this study two formulations of Clopidogrel had been evaluated. The mean ratio of parameters Cmax, AUC0-tand Tmax and 90% confidence intervals of correspondents were calculated to determine the bioequivalence.

The mean AUC0-t for reference and test formulation were 5585.81 and 6119.84 and for Cmax 3913.17 and 4185.67 ng/ml respectively. The 90% confidence intervals were 95-125% for AUC0-t and 85-133% for Cmax.

The AUC0-t is recognized as an uncontaminated measurement of the extent of absorption. The Cmax and

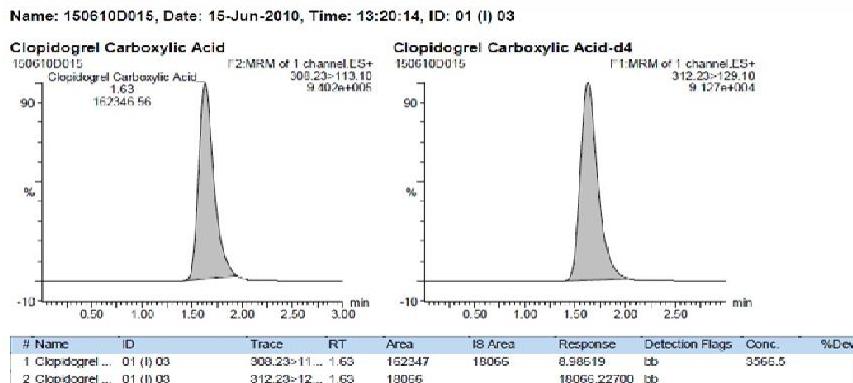


Figure 4. LC/MS/MS chromatogram showing maximum plasma concentration (C_{max}) for Clopidogrel metabolite after 0.66 hour of reference drug dosing (volunteer 1)

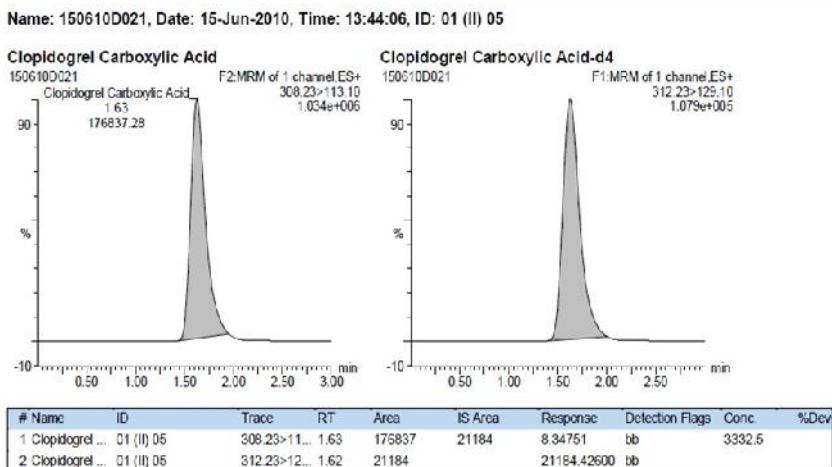


Figure 5. LC/MS/MS chromatogram showing maximum plasma concentration (C_{max}) for Clopidogrel metabolite after 1.33 hour of tested drug dosing (volunteer 1)

T_{max} are parameters that influenced by absorption rate. The 90% CI of mean AUC_{0-t} (after log-transformation of individual ratios) was included into the bioequivalence range (80-125%), consequently, the two formulations are equivalent for the extend of absorption.

The statistical comparison of C_{max} indicated significant difference in the two formulations. 90% CI for the mean ratio(T/R) of C_{max} was not within the US Food and Drug Administration and European Medicines Agency acceptance range[Center for Drug Evaluation and Reserch 2003, Committee for Property Medicinal Products 2001]. According to some regional regulations such as GCC regulations on Drug Bioequivalence, the two products could be considered bioequivalent in the rate and extent of absorption[6] . The method of analysis which used was simple and suitable to evaluate the

bioequivalence and clinical pharmacokinetic of clopidogrel.

CONCLUSION

Based on the 90% confidence intervals of the relative mean AUC_{0-t} and C_{max} of tested drug (Plofexine) to reference (Plavix), we can conclude that clopidogrel 75 mg tablet (Asia Pharm, Syria) is bioequivalent to Plavix 75 mg tablet (Sanofi-aventis), for the extend of absorption, and not bioequivalent for the rate of absorption, according to USFDA and EMEA regulations . But according to GCC regulations on Drug Bioequivalence, the two products considered bioequivalent in the rate and extent of absorption too. The method of analysis which used was simple and

suitable to evaluate the bioequivalence and clinical pharmacokinetic of clopidogrel.

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