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Bioequivalence Evaluation of Two brands of Clarithromycin 500 mg Tablets (*Clamycin* (Rithrocid) & *Klacid*) in Healthy Human Volunteers

Naji M. Najib, Nasir Idkaidek*, Muntaser Beshtawi*, Mohammed B.*, Isra'Admour*, S. Mahmood Alam†, Ruwayda Dham†*, and Qumaruzaman†*
** International Pharmaceutical Research Centre (IPRC), Amman - Jordan*
†Gulf Pharmaceutical Industries - Julphar, U.A.E.

Abstract

Objective To evaluate the bioequivalence of two oral formulations of 500 mg clarithromycin, *Clamycin (Rithrocid)* tablets (Julphar, UAE) and *Klacid* tablets (Abbott Lab., U.K.) in 24 healthy human volunteers by statistical analysis of the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as recommended by *FDA*.
Design Single dose, two-sequence, cross-over randomized design at International Pharmaceutical Research Centre (IPRC), Amman, Jordan.
Methods Both test and reference tablets were administered to each subject after an overnight fasting on two treatment days separated by one week washout period; blood samples were collected up to 36 hours and analyzed for clarithromycin by a sensitive, reproducible and accurate HPLC method with electro-chemical detection. Various pharmacokinetic parameters including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and λ_z were determined.
Results Pharmacokinetic parameters for both formulations were found to be in good agreement with reported values. AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were tested for bioequivalence after log-transformation of data. No significant difference was found based on ANOVA; 90% confidence interval (95.5-111.7% for AUC_{0-t}, 95.6-112.0 for $AUC_{0-\infty}$; 90.8-120.5% for C_{max}) for test/reference ratio of these parameters were found within *FDA* acceptance range of 80–125%.
Conclusion *Clamycin* was found bioequivalent to *Klacid* and interchangeable in medical practice.

Introduction

Bioequivalence of two formulations of the same drug is concluded based on the lack of difference in the rate (C_{max}) and extent of absorption *(AUC)* especially in conventional drug formulations.[1] In the present study bioequivalence of two clarithromycin tablets was evaluated by comparing those pharmacokinetic parameters derived from plasma concentration of clarithromycin.

Clarithromycin is a macrolide antibiotic derived from erythromycin through the substitution of an O-methyl group at position 6 of the lactone ring,[2, 3] improving the bioavailability by inhibiting decomposition under acidic conditions[4] and reduces the incidence of the adverse effects.[5] While comparing pharmacokinetic properties of erythromycin derivatives, clarithromycin shows advantages of increased bioavailability, increased plasma concentration and a longer elimination half-life.[6] Clarithromycin is well absorbed from the gastrointestinal tract and has an absolute bioavailability of 52-55%, and peak plasma concentrations of 2.41–2.85 µg/mL with 500mg dose.[6, 7] Clarithromycin is highly stable in the presence of gastric acid[8] the relatively lower bioavailability is due to the first pass metabolism effect which produces the 14-hydroxyclarithromycin.[9] Food delays the absorption of clarithromycin and the formation of this metabolite; however, the extent of absorption is not affected by food.[7, 10] Peak serum concentrations are achieved within 2 hours.[7, 11] Protein binding is low (42-50%), which may partially account for clarithromycin's extensive distribution relative to erythromycin.[9] Clarithromycin is metabolized to 14-OH clarithromycin, and roughly 20% of a dose is converted to this metabolite during first-pass metabolism.[7] Renal excretion is an important route of elimination for clarithromycin and its hydroxy metabolite. The renal clearance (mL/min) of clarithromycin is dependent on the dose.[7] As the dose increases (up to 1200 mg), renal clearance is decreased suggesting a saturable mechanism.[11] Elimination half-life for clarithromycin varies between 3-7 hours;[7] higher doses (eg, 500 mg versus 250 mg) are associated with the half-life in the upper range (i.e., 7 hours) due to the saturable metabolism.[11]

* To whom enquiries should be directed. Address: Gulf Pharmaceutical Industries, Julphar 1201, Twin Towers P.O. Box 42040, Dubai, U.A.E., Fax: 00971-4-2231122, email: julphard@emirates.net.ae

Material and Methods

Study Products

Test Product:	*Clamycin* - Clarithromycin 500 mg tablets
Batch No.:	0002, Expiry Date : 04/2002
	Gulf Pharmaceutical Industries - Julphar, United Arab Emirates
Reference Product:	*Klacid* - Clarithromycin 500 mg tablets
Batch No.:	51280VA, Expiry Date 03/2002
	Abbott Lab. U.K.

Study Subjects

Twenty-four (24) healthy adult male volunteers participated in this comparative study at Ibn Al-Haytham Hospital, Amman, Jordan, as joint venture with International Pharmaceutical Research Center (IPRC). Amman, Jordan. Their mean age was 22.1 ± 3.94 years; mean body weight was 70.6 ± 9.84 kg and mean body height was 174.5 ± 7.10 cm. The volunteers were free from significant cardiac, hepatic, renal, pulmonary, neurological, gastro-intestinal and haematological diseases, as determined by their medical history, physical examination, and routine laboratory tests (haematology, blood biochemistry, and urine analysis). This study was performed according to the revised Declaration of Helsinki for bio-medical research involving human subjects and the rules of Good Clinical Practices. The study protocol was approved by Institutional Review Board (IRB) of Ibn Al-Haytham Hospital, Amman, Jordan.

Drug administration and sample collection

After an overnight fasting (10 hours) subjects were given single dose of either formulation (reference or test in a randomized fashion) of clarithromycin 500 mg tablet with 240mL of water; fasting was continued until 5 hours after ingestion of the dose. Approximately 10 mL of blood samples for clarithromycin assay were drawn into evacuated heparinized glass tubes through indwelling cannula before (0 hr) and at 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours after dosing. Blood samples were centrifuged at 3500 rpm for 10 minutes; plasma was transferred directly into 5 mL plastic tubes and stored frozen at –20°C pending drug analysis. After a period of 7 days study was repeated in the same manner to complete the crossover design.

Chromatographic conditions

Plasma samples were analyzed for clarithromycin according to a sensitive, selective and accurate HPLC method, which was developed and validated before the study. The HPLC system was from Shimadzu Kyoto, Japan, and it consisted of a solvent delivery pump (LCD-10AD), a system controller (SCL-10A), an auto-injector (SIL-10A), and an electrochemical detector (L-ECD-6A); integration was done using Class VP-5 software version 5.03. Chromatographic separation was performed using Symmetry C_8 (4.6 x 100 mm), 3.5 µm particle size, HPLC cartridge column. The mobile phase consisted of 36% acetonitrile and 64% phosphate buffer, and eluted at a flow rate of 1.2 mL/min at a constant oven temperature of 40°C. The effluent was monitored using an electrochemical detector (ECD). The peak area were measured, and the peak area ratio of drug to internal standard and the concentration were calculated by Class VP-5 software (version 5.03) Shimadzu. Each analysis required a maximum of 12 minutes. The method was validated by following international guidelines.[12]

Sample preparation for HPLC injection

50µL of the internal standard working solution (azithromycin 4.0 µg/mL) was added to 0.5 mL plasma sample. The samples were vortexed for 30 seconds, 250 µL of 0.1M sodium carbonate were added

then samples were vortexed for 30 seconds. 6 mL of extraction solvent (tert-butylmethyl ether) was added and vortexed for one minute then centrifuged for 5 minutes at 3000 rpm. The supernatant (organic layer) was transferred to another 10 mL glass tube and evaporated to dryness at 40°C under nitrogen, then reconstituted with 200µL of mobile phase and transferred to eppendorf tube (0.75 mL), and centrifuged for 2 minutes. 100µL aliquot sample was injected into a Symmetry C_8 (4.6 x 100 mm), 3.5µm particle, HPLC cartridge column, where clarithromycin and internal standard were separated from endogenous substances.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic analysis was performed by means of model independent method using KineticaTM 2000 computer program.[13] To assess the bioequivalence between two formulations, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were considered as the primary variables. Two way analysis of variance (ANOVA GLM procedure; KineticaTM 2000 Computer program)[13] for crossover design was used to assess the effect of formulations, periods, sequences and subjects on these parameters. Difference between two related parameters was considered statistically significant for p-value equal to or less than 0.05. Parametric 90% confidence intervals[14] based on the ANOVA of the mean test/reference (T/R) ratios of *AUCs* and C_{max} were computed.

Results and Discussion

Clarithromycin was well tolerated by the volunteers; unexpected incidents that could have influenced the outcome of the study did not occur. There was no drop-out and all volunteers who started the study continued to the end and were discharged in good health. The described analytical method was proven sensitive and accurate for determination of clarithromycin in plasma.

Both formulations were readily absorbed from the gastrointestinal tract and clarithromycin was measurable at the first sampling time (0.33 hour) in most of the volunteers. The mean concentration-time profile of the two formulations is shown in the Figure 1. Peak concentration were attained at 1.89 and 1.88 hours after drug administration and then declined rapidly but were still detectable up till 36 hours. All calculated pharmacokinetic parameter were in good agreement with reported values.[3, 7, 9, 11]

Table 1 shows the pharmacokinetic parameters for the two brands of clarithromycin 500mg tablets. The relative bioavailability of *Clamycin* was 105.7% for AUC_{0-t}, 105.8% for $AUC_{0-\infty}$, and 113.8% for C_{max}.

The mean and standard deviation of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the two products did not differ significantly, suggesting that the blood profiles generated by *Clamycin (Rithrocid)* are comparable to those produced by *Klacid*. Table 2 shows statistical results; analysis of variance (ANOVA) for these parameters, after log-transformation of the data, showed no statistically significant difference between the two formulations either in periods, formulations or sequence, having p value greater than 0.05. 90% confidence intervals also demonstrated that the ratios of AUC_{0-t}, $AUC_{0-\infty}$ or C_{max} of the two formulations lie within the *FDA* acceptable range of 80–125%.

For T_{max} the parametric point estimate of difference (test – reference) was 0.01 h, and found to be within the acceptance limits (± 20% of reference mean).

Plasma levels may be used as surrogate parameters for clinical activity; therefore results of this study suggest equal clinical efficacy of the two brands of clarithromycin.

Conclusion

Statistical comparison of the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} clearly indicated no significant difference between two studied brands in any of the calculated pharmacokinetic parameters. Based on the above we can conclude that *Clamycin (Rithrocid)*, manufactured by Gulf Pharmaceutical Industries, U.A.E. is bioequivalent to *Klacid*, manufactured by Abbott Laboratories, UK, and that both products can be considered equally effective in medical practice.

Table 1 Pharmacokinetic Parameters of Clarithromycin 500 mg Tablets (mean ± standard deviation, n = 24)

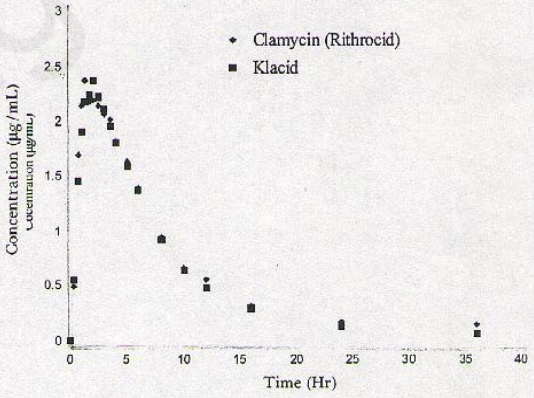
Pharmacokinetic	*Clamycin* (Test)	*Klacid* (Reference)
AUC_{0-t} (µg/mL.hr)	19.85 ± 10.21	18.82 ± 8.12
$AUC_{0-\infty}$ (µg/mL.hr)	21.05 ± 11.23	20.19 ± 8.53
C_{max} (µg/mL)	2.70 ± 1.15	2.66 ± 1.33
T_{max} (Hr)	1.89 ± 1.16	1.88 ± 0.79
$t_{1/2}$ (Hr)	5.97 ± 2.07	6.30 ± 1.94
λ_z (/Hr)	0.13 ± 0.05	0.12 ± 0.05

Table 2 Statistical Analysis of Log-transformed data

Statistical analysis	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
ANOVA GLM (P-value)	0.4503 (0.0354)	0.4384 (0.050)	0.5938 (0.2920)
90% CI	95.5 – 111.7%	95.6 – 112.0%	90.8 – 120.5%

Parenthesis values indicate analysis for periods.

Fig 1 Mean Plasma Concentrations of Clarithromycin After Oral Administration (500 mg) of the Two Brands to 24 Healthy Human Volunteers



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