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Title: Comparative single-dose bioavailability study of two 500 mg clarithromycin tablet formulations in healthy volunteers under fasting condition

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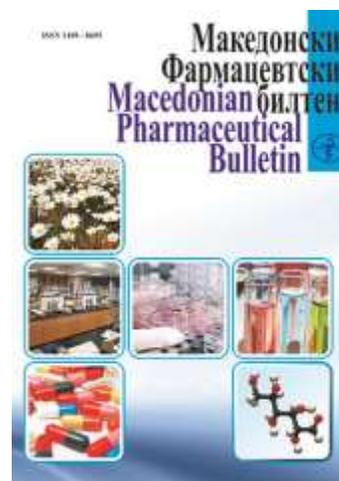
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Comparative single-dose bioavailability study of two 500 mg clarithromycin tablet formulations in healthy volunteers under fasting condition

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Abstract

Clarithromycin is a semi-synthetic macrolide antibiotic, chemically 6-O-methylerythromycin, formulated as immediate-release tablets, extended-release tablets, and granules for oral suspension.

The objective of this study was to evaluate and compare the relative bioavailability, and therefore the bioequivalence of Clarithromycin 500 mg test formulation versus a reference Klacid[®] forte 500 mg formulation, following a single dose administration under fasting conditions.

The study was a single center, open, single dose, randomized, two-way crossover study in healthy male volunteers, with a wash-out period of one week between study periods. Twenty-four male healthy volunteers, aged 18-49 years were included into study. Blood samples for determination of clarithromycin and 14-OH clarithromycin concentrations were withdrawn at zero (pre-drug administration), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 and 36 hours post-drug administration.

The determination of clarithromycin and 14-OH clarithromycin concentrations in plasma was performed using validated LC/MS/MS method and internal standardization after liquid/liquid extraction with methyl t-butyl ether.

The test formulation of clarithromycin, dosed at 500 mg is bioequivalent for primary clarithromycin and 14-OH clarithromycin parameters (C_{max} , AUC_{0-t} and $AUC_{0-\infty}$) to the reference formulation after a single oral administration of 500 mg clarithromycin. Both medications were well tolerated with no serious adverse events. Thus, in view of the clinical use, both formulations are exchangeable without restrictions.

Keywords: clarithromycin, 14-OH clarithromycin, bioavailability, bioequivalence study, single-dose

Introduction

Clarithromycin is a semi-synthetic macrolide antibiotic, chemically 6-O-methylerythromycin, with molecular formula $C_{38}H_{69}NO_{13}$, molecular weight of 747.96, formulated as immediate-release tablets, extended-release tablets, and granules for oral suspension. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms, resulting in inhibition of protein synthesis and showing *in vitro* activity against a variety of aerobic and anaerobic Gram-positive and Gram-negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms. The 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity showing twice as active against *Haemophilus influenzae* microorganisms as the parent compound clarithromycin and 4 to 7 times less active to *Mycobacterium avium* complex (MAC) isolates. So, clarithromycin is used against following microorganisms: aerobic Gram-positive microorganisms (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*), aerobic Gram-negative microorganisms (*Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Mycobacterium avium* complex (MAC) (Dinos, 2017; Fraschini et al., 1993).

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration and food slightly delays the onset of absorption (from 2 to 2,5 hours), with increase of peak plasma

concentration by about 24%, but it does not affect the extent of bioavailability (Alkhalidi et al., 2019; Frascini et al., 1993; Padovan et al., 2012; Quinney et al., 2013). Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration, but does slightly decrease the extent of metabolite formation (Frascini et al., 1993; Radwan et al., 2019).

The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The elimination half-life of the principal metabolite, 14-OH clarithromycin, in dosing every 12 hours with 250 mg dose was 5-6 hours, while in dosing every 8-12 hours with 500 mg dose was 7-9 hours. The renal clearance of clarithromycin is relatively independent of the dose size and approximates the normal glomerular filtration rate. The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects (Alkhalidi et al., 2019; Dinos, 2017; Frascini et al., 1993; Radwan et al., 2019).

Study objective

The objective of this study was to evaluate and compare the relative bioavailability, and therefore the bioequivalence of tablets Clarithromycin[®] 500 mg REPLEKFARM DOO Skopje AD (test formulation) with Klacid[®] forte (ABBOTT GmbH & Co, Germany) 500 mg tablets, using a randomized two-way crossover study in 24 healthy male volunteers after single oral dose under fasting conditions.

Materials and methods

Experimental design of the study

The study was a single center, open, single dose, randomized, balanced, two-way crossover study in 24 healthy male volunteers with a wash - out period of one week between study periods (Directive 2001/20/EC, 2001; EMEA/CPMP/ICH/135/95, 1997).

Selection of study population

Twenty-four male healthy volunteers, aged 18-49 years, with ideal body weight according to the Body Mass Index 18-30, non-smokers, were included into study. The volunteers' health condition was established on the base of medical history, physical examination, biochemical and hematological tests.

The study was started after the Ethical Committee for Medical Investigations and the Bureau for Medicines, Ministry of Health, Republic of North Macedonia, had given their approval in writing.

A sample of 24 subjects was estimated to be sufficient for the bioequivalence assessment of the investigated clarithromycin under fasting conditions. The sample size was calculated in respect to the primary target parameter $AUC_{0-\infty}$ and C_{max} from the literature data. If in addition to a consumer risk of <5%, a coefficient of variation of 18.5% and a mean difference of 5% between the preparations are taken into consideration, a total number of minimum 17 volunteers will be needed in order to prove bioequivalence with a power of 80%. In the case of bioequivalence trials, the power is only of limited importance since it is a value, which represents the probability to prove existing bioavailability and as such is usually regarded as "producer risk". A total number of 24 volunteers were enrolled.

Prior to entering the study, the volunteers were informed about the administered preparations and the possible risk for their health. All of them signed the "Informed consent".

Inclusion criteria

The subjects who fulfilled the following criteria were eligible for this trial:

- Healthy male volunteers;
- Caucasian race;
- Age between 18 and 55 years;
- Ideal body weight according to the Body Mass Index 18-28 kg/m²;
- Non-smokers;
- Clinically normal vital signs;
- Clinically normal medical history;
- Clinically normal findings on physical examination;

- Clinically normal findings for haematology and clinical chemistry of blood and urine or showing clinically insignificant deviations only. These assessments involve (quantitative) measurements of the following;
- Able to communicate and co-operate with the investigator and his staff;
- Signed Informed consent prior to participation in the study.

The above listed analyses were performed within 14 days of the study start.

Exclusion criteria

Subjects meeting one or more of the following criteria were not eligible:

- History of alcohol and/or drug abuse within the past 1 year;
- Presence of any clinically significant illness, particularly gastrointestinal, liver or kidney disease, or any other conditions that may affect drug bioavailability;
- History of any clinically significant illness, particularly gastrointestinal, liver or kidney disease, or surgery that that may affect drug bioavailability;
- Clinically significant abnormalities on physical examination, of the ECG or haematology, biochemistry and urinalysis results;
- Positive cotinine test;
- Positive screen for drugs of abuse;
- Positive screen for HBsAg, anti-HCV, anti-HIV-1/HIV-2;
- Seated systolic blood pressure below 110 mmHg and/or diastolic below 60 mmHg at screening;
- Sitting heart rate below 55 beats/minute at screening;
- Use of vitamins or herbal products within 2 weeks before the study;
- Use of any other over-the-counter medication or prescription medication within 4 weeks before the study;
- Subjects who have a known sensitivity to study drug or any similar drugs as well as severe hypersensitivity reactions (like angioedema) to any drugs;
- Participation in other clinical studies within 2 months before this study;
- Donation or loss of more than 450 mL of blood within 2 months, or donation of plasma or platelets within 2 weeks before the study;

- Unable or unwilling to comply with the provisions of this protocol.

Study medication information

In the study, as a test drug (T), Clarithromycin 500 mg tablets, product of ReplekFarm doo was used. Reference drug (R) was Klacid[®] forte 500 mg tablets, product of ABBOTT GmbH & Co, Germany. The formulations were administered in fasting conditions. Drugs were administered orally in the form of tablets with 240 mL of room temperature water. The volunteers received the tested formulations according to the randomization scheme. After wash-out period of 7 days, the other drug was administered.

Sample collection and drug concentration measurement

Blood samples for determination of clarithromycin and 14-OH clarithromycin were withdrawn at zero (pre-drug administration), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 and 36 hours post-drug (16 blood samples).

The concentrations of clarithromycin and 14-OH clarithromycin were performed in internal standardization mode after liquid/liquid extraction with methyl t-butyl ether. Detection was carried out on a tandem mass spectrometer with positive electrospray ionization and SRM - MS/MS monitoring of the protonated molecular ions of drug, metabolite and internal standard, decomposing under controlled conditions to the most dominant respective fragments. The lower limit of quantification (LLOQ) was established at 1.078 µg/L for clarithromycin and 0.358 µg/L for 14-OH-clarithromycin with an upper limit of quantification (ULOQ) of 1725 µg/L for clarithromycin and 572.5 µg/L for 14-OH-clarithromycin. Analysis of calibration standards confirmed that the assay was linear over this range. The calibration curve and standards and the quality control standards met the acceptance criteria demonstrating acceptable performance of the method.

Bioequivalence/Bioavailability parameters

According to the obtained plasma concentrations/time data of clarithromycin and 14-OH clarithromycin the following pharmacokinetic parameters were calculated using software KINETICA™ 4.2 (Innaphase corporation, USA):

Primary parameters: AUC_{0-t} and $AUC_{0-\infty}$ (area under the curve of the plasma concentrations until the last sampling time and infinity), C_{max} (maximum plasma concentration).

Secondary variable: T_{max} (time of reaching the maximum plasma concentrations).

Statistical analysis

The correspondent 90% confidence intervals for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} of the tested preparation as a ratio to the correspondent values of the referent preparation using parametric and nonparametric methods without or with log-transformation of data were calculated for clarithromycin and 14-OH clarithromycin. The differences in T_{max} of test and reference preparations were analysed by means of a non-parametric analysis of variance at a 90% confidence interval (Diletti et al., 1991, Schuirmann, 1987). Using the multiplicative model, bioequivalence is assumed when the 90% confidence interval of the point estimate (test over reference formulation) falls inside 80-125% for AUC and for C_{max} range.

Results and discussion

Twenty-six (26) male Caucasian subjects were recruited for participation in the trial. Among the 26 subjects recruited for the trial, twenty-four (24) were included in the study. There was no drop out.

Demographic data from the study shows that participants have mean \pm SD age (29.92 \pm 10.18), weight (83.71 \pm 9.21), height (177.67 \pm 8.04), and body mass index (26.47 \pm 1.67).

The maximum plasma concentrations of clarithromycin (1576.08 \pm 457.92 μ g/L) and (1665.08 \pm 305.23 μ g/L) was attained in about 1.97 \pm 1.08 hours and 1.88 \pm 0.73 for both test and reference, respectively. Area under the curve (AUC_{0-36}) mean \pm SD values were 14341.62 \pm 3444.94, and 14847.64 \pm 3627.72 μ g/L x h for both test and reference tablets. Total area under the curve ($AUC_{0-\infty}$) mean \pm SD values were 14511.02 \pm 3530.31, and 15018.5 \pm 3821.91 μ g/L x h for both test and reference tablets.

The maximum plasma concentrations of 14-OH-clarithromycin (700.9304 \pm 232.78 μ g/L) and (700.9333 \pm 237.79 μ g/L) was attained in about 2.28 \pm 1.02 hours and 2.38 \pm 1.30 for both test and reference, respectively. Area under the curve (AUC_{0-36}) mean \pm SD values were 8255.13 \pm 1733.10, and 8374.49 \pm 1946.46 μ g/L x h for both test and reference tablets. Total area

under the curve $AUC_{0-\infty}$ mean \pm SD values were 8668.67 ± 1866.22 , and 8717.951 ± 2005.71 $\mu\text{g/L} \times \text{h}$ for both test and reference tablets.

The primary and secondary pharmacokinetic parameters (mean \pm SD) are presented in Tables 1, 2, 3, 4, 5 and 6 for test and reference formulations.

Table 1

Table 2

Table 3

Table 4

Figures 1, 2, 3 and 4 illustrate the mean plasma concentration time-course of clarithromycin and 14-OH-clarithromycin obtained after the administration of 500 mg clarithromycin as treatment A (Test) and treatment B (Reference) in the twenty-four healthy young male volunteers, in linear and semi-logarithmic scale.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Statistical analysis

The results of the statistical analysis of the pharmacokinetic parameters of clarithromycin and 14-OH-clarithromycin between the test and reference formulations are resumed in the table 5 and 6.

Table 5

Table 6

Safety

Both medications were well tolerated by all subjects without adverse events. Vital signs showed no marked changes throughout the study. Clinical laboratory and hematology parameters

checked at the end of the study were in the normal range of values.

Analysis of pharmacokinetic parameters

From the 24 subjects included in this study, 24 were analyzed and included in the pharmacokinetic and statistical analysis for the clarithromycin and 14-OH-clarithromycin.

After the administration of 500 mg clarithromycin as test and reference formulations, the mean plasma concentration time-courses of clarithromycin and 14-OH-clarithromycin present the same pharmacokinetic profiles with minor differences between the two formulations.

The statistical analysis of the half-life of elimination, clearance, rate of elimination and mean residence time showed no significant difference between the values of test and reference formulation.

Safety analysis

All the subjects included in this study (24 subjects) were considered for the safety analysis. Both treatments (Treatment A and Treatment B) appear to be safe and well tolerated after single oral dose of clarithromycin 500 mg tablet to healthy male volunteers under fasting conditions. No death or serious adverse event did occur during the study.

The safety analysis shows that both treatments were well tolerated without any adverse events during both periods.

Conclusion

As conclusion, the test formulation dosed at 500 mg is bioequivalent for primary clarithromycin and 14-OH-clarithromycin parameters (C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ parameters) to the reference formulation after a single oral administration of 500 mg clarithromycin. The peak plasma concentration of clarithromycin and 14-OH-clarithromycin (C_{max}) is approximately equal in both formulations and the AUC parameters are bioequivalent to the reference formulation.

Both medications were well tolerated with no adverse events. Thus, in view of the clinical use, both formulations are exchangeable without restrictions.

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Резиме**Компаративна студија на биорасположивост на две формулации на кларитромицин во форма на таблети од 500 mg по еднакратна апликација кај здрави доброволци**

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Клучни зборови: кларитромицин, 14-ОН-кларитромицин, биорасположивост, биоеквивалентна студија, еднакратна доза

Кларитромицин е полусинтетски антибиотик од групата на макролидни антибиотици, хемиски е 6-О-метилеритромицин, а како фармацевтски формулации е расположлив во форма на таблети со брзо ослободување, таблети со продолжено ослободување и гранули за перорална суспензија.

Целта на оваа студија беше да се евалуира и спореди релативната биорасположивост, а потоа и биоеквивалентноста на кларитромицин од тест формулацијата од 500 mg во однос на референтна формулација Klacid[®] forte од 500 mg по нивна еднакратна примена на гладно.

Студијата беше спроведена како моноцентрична, отворена, со еднакратна апликација, рандомизирана, двојно вкрстена студија кај здрави машки доброволци со “wash-out” период од една недела меѓу двата периоди. Дваесет и четири машки здрави доброволци на возраст од 18-49 години беа вклучени во студијата. Примероците на крв за

одредување на плазматските концентрации на кларитромицин и 14-ОН-кларитромицин беа земани во време нула (пред примена на лекот), 0,33; 0,66; 1; 1,5; 2; 2,5; 3; 3,5; 4; 5; 6; 8; 12; 24 и 36 часа по примена на лекот.

Плазматските концентрации на кларитромицин и 14-ОН-кларитромицин беа одредувани со валидирана LC-MS-MS метода со користење на интерен стандард и течно-течна екстракција со метил-t-бутил етер.

Испитуваната формулација на кларитромицин во доза од 500 mg е биоеквивалентна во однос на примарните параметри на кларитромицин и 14-ОН-кларитромицин (C_{max} , AUC_{0-36} и $AUC_{0-\infty}$) во однос на референтната формулација по еднакратна орална примена на кларитромицин во доза од 500 mg. Двата дадени лека покажаа добра подносливост и не беа забележани несакани настани за време на испитувањето. Поради тоа може да се заклучи дека двете формулации се меѓусебно заменливи без никакви ограничувања.

Table 1. Mean pharmacokinetic parameters of clarithromycin (Test)

Formulation	CLARITHROMYCIN (TEST)					
Parameter	n	Mean	Median	Min	Max	SD
AUC _{0-∞} (µg/L × h)	24	14511.02	13617.05	9260.53	21862.7	3530.31
AUC ₀₋₃₆ (µg/L × h)	24	14341.62	13546.75	9083.8	21420.2	3444.94
C _{max} (µg/L)	24	1576.08	1535.58	516.81	2439.06	457.52
T _{max} (h)	24	1.97	2.0	0.66	6.0	1.08

Table 2. Mean pharmacokinetic parameters of 14-OH-clarithromycin (Test)

Formulation		CLARITHROMYCIN (TEST)				
Parameter	n	Mean	Median	Min	Max	SD
$AUC_{0-\infty}$ ($\mu\text{g/L} \times \text{h}$)	24	8668.67	8394.52	4056.01	12438.50	1866.22
AUC_{0-36} ($\mu\text{g/L} \times \text{h}$)	24	8255.13	8066.72	3837.94	11366	1733.10
C_{max} ($\mu\text{g/L}$)	24	700.9304	637.94	316.10	1293.11	232.78
T_{max} (h)	24	2.28	2.5	0.66	5.0	1.02

Table 3. Mean pharmacokinetic parameters of clarithromycin (Reference)

Formulation	KLACID® FORTE (REFERENCE)					
Parameter	N	Mean	Median	Min	Max	SD
AUC _{0-∞} (µg/L × h)	24	15018.58	14522.70	8359.19	26017.60	3821.91
AUC ₀₋₃₆ (µg/L × h)	24	14847.64	14422.75	8320.27	24649.70	3627.72
C _{max} (ng/mL)	24	1665.08	1700.88	876.69	2057.59	305.23
T _{max} (h)	24	1.88	2.0	1.0	4.0	0.73

Table 4. Mean pharmacokinetic parameters of 14-OH-clarithromycin (Reference)

Formulation	KLACID® FORTE (REFERENCE)					
Parameter	N	Mean	Median	Min	Max	SD
AUC _{0-∞} (µg/L × h)	24	8717.951	8673.32	4865.21	12397.70	2005.71
AUC ₀₋₃₆ (µg/L × h)	24	8374.49	8324.21	4666.48	12208.80	1946.46
C _{max} (ng/mL)	24	700.9333	657.26	392.98	1257.69	237.79
T _{max} (h)	24	2.38	2.25	1.0	6.0	1.30

Table 5. Statistical analysis of the pharmacokinetic parameters of clarithromycin

Test for the statistical comparison	T _{max}	C _{max}	AUC ₀₋₃₆	AUC _{0-∞}
Wilcoxon test	NS	/	/	/
ANOVA				
Treatment	/	N.S. (p>0.05)	N.S. (p>0.05)	N.S. (p>0.05)
Subject	/	N.S. (p>0.05)	N.S. (p>0.05)	N.S. (p>0.05)
Period	/	N.S. (p>0.05)	N.S. (p>0.05)	N.S. (p>0.05)
		Bioequivalence test		
90% standard confidence interval	/	0.8239-1.0509	0.9132-1.0222	0.9145-1.0239
Two one-sided T-tests (Schuirmann)	/	equivalence can be concluded	equivalence can be concluded	equivalence can be concluded

Table 6. Statistical analysis of the pharmacokinetic parameters of 14-OH- clarithromycin

Test for the statistical comparison	T _{max}	C _{max}	AUC ₀₋₃₆	AUC _{0-∞}
Wilcoxon test	NS	/	/	/
ANOVA				
Treatment	/	N.S.(p>0.05)	N.S.(p>0.05)	N.S.(p>0.05)
Subject	/	NS (p>0.05)	N.S.(p>0.05)	N.S.(p>0.05)
Period	/	N.S. (p>0.05)	N.S.(p>0.05)	N.S.(p>0.05)
Bioequivalence test				
90% standard confidence interval	/	0.9053-1.1056	0.9403-1.0392	0.9490-1.0458
Two one-sided T-tests (Schuirmann)	/	equivalence can be concluded	equivalence can be concluded	equivalence can be concluded

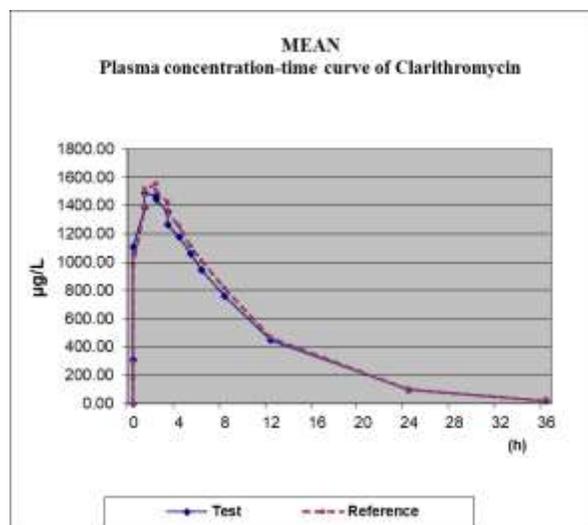


Fig. 1. Mean plasma concentration-time curve of clarithromycin after single administration of test and reference formulation of 500 mg clarithromycin.

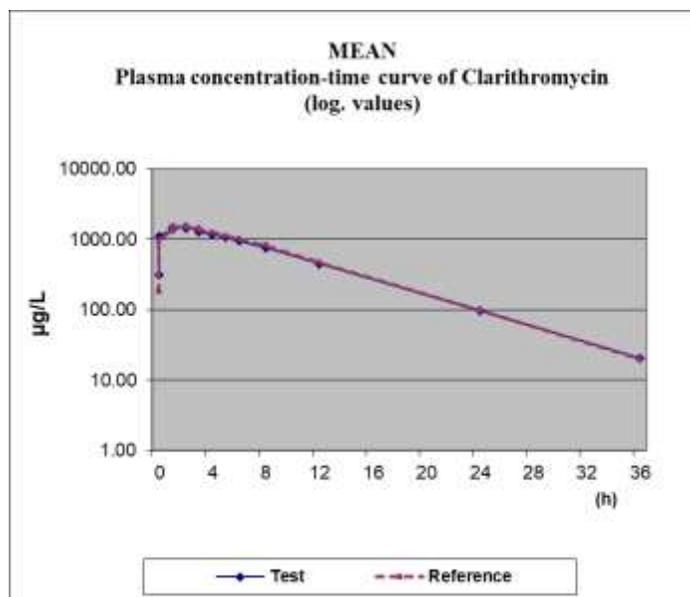


Fig. 2. Mean plasma concentration-time curve of clarithromycin (log. values) after single administration of test and reference formulation of 500 mg.

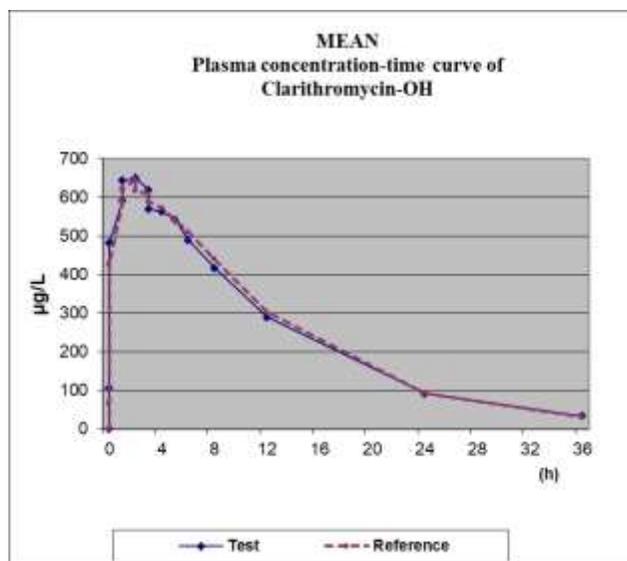


Fig. 3. Mean plasma concentration-time curve of 14-OH-clarithromycin after single administration of test and reference formulation of 500 mg clarithromycin.

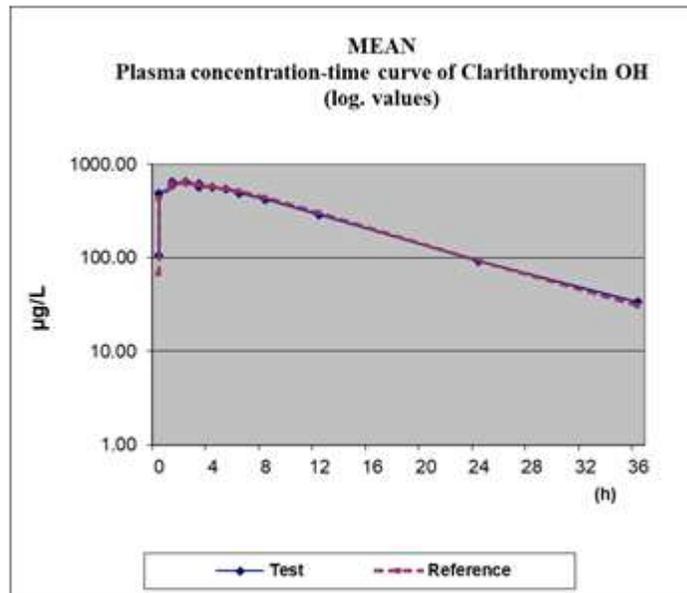


Fig. 4. Mean plasma concentration-time curve of 14-OH-clarithromycin (log. values) after single administration of test and reference formulation of 500 mg.

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