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Absolute Bioavailability of Clarithromycin after Oral Administration in Humans

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The absolute bioavailability of clarithromycin, a new macrolide antimicrobial agent, was assessed in a three-way, randomized, single-dose, crossover study conducted with 22 healthy volunteers, 19 of whom provided analyzable study data. The bioavailability parameters of two 250-mg oral tablet formulations were calculated with reference to an identical dose administered by intravenous infusion of the lactobionate salt. After adjustment for formulation potency, the mean absolute bioavailabilities of the two oral formulations were 52 and 55%, on the basis of the appearance of parent compound in the systemic circulation. Metabolite peak concentration and area under the plasma concentration-time curve data after oral dosing were generally greater than those after intravenous infusion, suggesting that marked first-pass metabolism of clarithromycin occurs after oral administration. Pharmacokinetic analysis of the parent drug and the active 14-hydroxy metabolite data suggests complete (or nearly complete) absorption of the drug after oral administration.

Clarithromycin is a new 14-membered macrolide antimicrobial agent that exhibits a broad spectrum of antimicrobial activity against gram-positive and -negative aerobes and anaerobes. Susceptible pathogens include staphylococci, streptococci, *Haemophilus influenzae*, *Legionella pneumophilia*, *Mycobacterium* species, *Chlamydia* and *Mycoplasma* species, and anaerobes (2, 3, 7–9, 13, 14, 17). In addition, the 14-hydroxy metabolite of clarithromycin appears to have antimicrobial activity which may be additive or synergistic to that of the parent compound (9).

This study was designed to evaluate the absolute bioavailability of clarithromycin from two identical 250-mg oral tablet formulations (utilizing two different batches of bulk drug) with an intravenous (i.v.) infusion of the lactobionate salt as a reference. Study subjects were males between the ages of 18 and 40 years (inclusive) and were judged to be in good health on the basis of results of medical history, physical examination, ophthalmologic examination, laboratory profile, and electrocardiographic evaluations. Exclusion criteria included history of allergy or sensitivity to any antibiotic, requirement for any medication on a regular basis, blood or plasma donation within 2 months prior to study entry, and history of drug abuse. All subjects provided written, informed consent, as approved by the Institutional Review Board of Quincy Research Center, Kansas City, Mo., prior to participation. Subjects were confined in the study facility from the morning prior to each dosing until collection of the 24-h blood sample.

The study was conducted as a three-way, randomized, crossover design in which each subject received a single 250-mg dose of clarithromycin (formulation 1, 250-mg oral tablet, batch 1; formulation 2, 250-mg oral tablet, batch 2; and formulation 3, 250-mg i.v. infusion of the lactobionate salt) on three separate occasions separated by a 1-week washout period. The sequences of formulation assignment (1-2-3, 2-3-1, and 3-1-2) were assigned to the subjects by using a computer-generated randomization scheme. The oral formulations were administered with 240 ml of water, and the i.v. formulation (diluted to a concentration of 1 mg/ml) was infused over 45 min. On each dosing day, drug administration occurred after a 12-h overnight fast. Subjects were served breakfast 2 h after drug administration, lunch was given after the h 6 blood collection, and dinner was served after the h 10 blood collection. Breakfast consisted of 4 oz (1 oz = 29.573 ml) of orange juice, two scrambled eggs, one slice of ham, two slices of toast, and one cup of coffee or skim milk, while lunch consisted of 1½ cups of pork-fried rice, two egg rolls, ½ cup of stir-fried vegetables, ½ cup of fruited jello salad, two almond cookies, and Kool-Aid.

Blood samples (7 ml) were collected (from the arm contralateral to the i.v. infusion site during the i.v. study phase) prior to dosing and at 0.33, 0.75, 1, 1.5, 2.5, 4, 6, 8, 10, 12, 14, and 24 h after oral administration or commencement of the i.v. infusion. Plasma was separated and stored frozen at −20°C until analysis.

The concentrations of clarithromycin and 14-hydroxyclarithromycin in plasma were determined by using a validated high-performance liquid chromatography method. In brief, plasma samples supplemented with internal standard (erythromycin A 9-*O*-methyloxime) were extracted with ethyl acetate-hexane (1:1). The chromatography was conducted with a reverse-phase C-8 column (5 μm, 4.6 mm [inner diameter] by 25 cm; Spherisorb; Phenomenex, Rancho Palo Verdes, Calif.), typically with a mobile phase consisting of acetonitrile (48% [vol/vol]), methanol (10%), 0.04 M acetic acid, and NaOH to produce a pH of 7.5. The effluent was monitored via electrochemical detection (model 5100 A; Environmental Sciences Associates, Bedford, Mass.) with the electric potentials of the first and second electrodes set at +0.5 and 0.78 ± 0.04 V, respectively. The lower limit of detection for both compounds was 0.03 mg/liter in plasma. The relative standard deviations for both compounds within-day and between-day were typically less than 7% (4).

Pharmacokinetic parameters for both the parent compound and the 14-hydroxy metabolite were derived by using both noncompartmental and model-dependent approaches (6). Peak concentration (C_{max}) and time to C_{max} (T_{max}) were obtained by visual inspection of the observed plasma concentration-time curve. Area under the plasma concentration-

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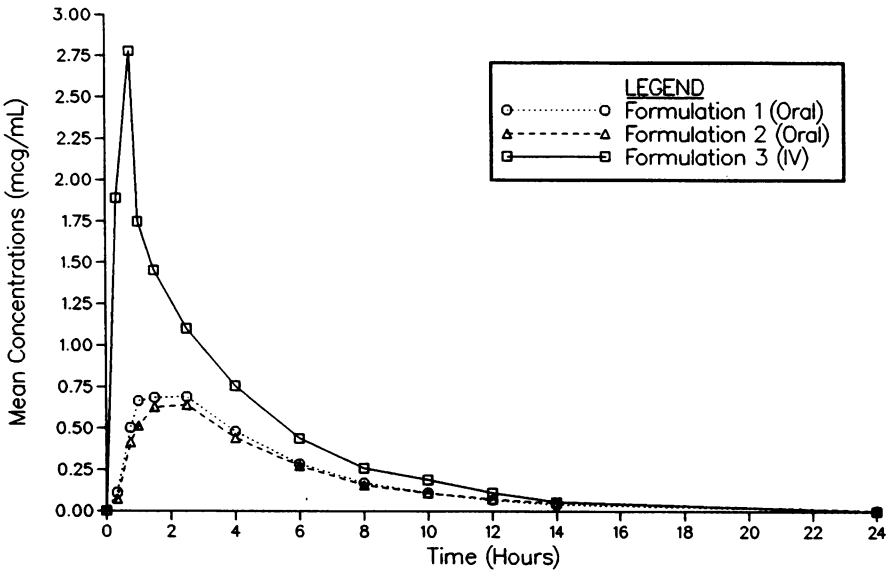

FIG. 1. Mean clarithromycin concentration-time profiles (in plasma) after oral and i.v. administration of 250 mg of clarithromycin. Standard deviation bars were omitted for purposes of clarity.

time curve from time 0 to 24 h postdose (AUC_{0-24}) was obtained by trapezoidal integration. Plasma concentration-time data were also subjected to curve stripping by using CSTRIP (16) and then to nonlinear regression by using the NONLIN 84 computer program (Statistical Consultants, Lexington, Ky.). Best-fit equations were based mainly on the Akaike Information Criterion (1), although the sum of weighted squared residuals and visual inspection of the fitted versus observed curves were also taken into consideration. By using the elimination rate constants generated from the model-dependent analysis, terminal elimination half-life ($t_{1/2}$), trapezoidal AUC_{0-24} extrapolated to infinity ($AUC_{0-\infty}$), total body clearance (CL; i.v. formulation only) and volume of distribution using the area method (V; i.v. formulation only) were calculated by using noncompartmental methods. As the mean AUC_{0-24} was ≥95% of the respective $AUC_{0-\infty}$ for all three formulations, AUC_{0-24} data were used in the bioavailability assessments (see below).

Analysis of variance with sequence, subject within sequence, period, and formulation effects was used to compare the pharmacokinetic parameters between formulations. Absolute bioavailability (formulations 1 and 2 versus 3) of clarithromycin was evaluated by using ratios of adjusted mean AUC_{0-24} (orally or i.v.) and analysis of variance to obtain a 90% confidence interval for the differences in the AUC_{0-24} between formulations. Statistical analyses were performed by using the Statistical Analysis System program (15). Data are presented as means (± standard deviations) unless otherwise noted.

Twenty of the twenty-two healthy adult male volunteers enrolled completed all three study phases. Two subjects failed to complete participation for non-study-related reasons. Data for one subject were excluded because of anomalous parent compound determinations secondary to chromatographic interferences, leaving data from 19 subjects suitable for the bioavailability analyses. The 19 subjects included in the bioavailability analyses ranged in age from 18 to 40 years (29 [± 6] years), in height from 164 to 188 cm (175 [± 8] cm), and in weight from 57.7 to 87.7 kg (71.5 [± 8.3] kg).

Fifteen subjects (68%) reported 21 adverse events during the course of the study. One subject reported one adverse event (somnolence) following administration of formulation 1, one subject reported one adverse event (nausea) following administration of formulation 2, and 13 subjects reported 19 adverse events (mainly infusion site related) following administration of formulation 3. None of the adverse events reported during the study required treatment.

Figures 1 and 2 illustrate the mean plasma concentration-time curves for clarithromycin and 14-hydroxyclarithromycin after oral and i.v. administration of identical 250-mg clarithromycin doses, respectively. Tables 1 and 2 delineate the pharmacokinetic parameters and bioavailability analyses, respectively. The plasma concentration-time profiles after oral dosing were best fit by using a one-compartment pharmacokinetic model with first-order input and monoexponential elimination, while the i.v. dosing data were best fit by using a two-compartment pharmacokinetic model with constant rate input.

After oral dosing with 250 mg of clarithromycin, clarithromycin was rapidly absorbed, with mean T_{max} for formulations 1 and 2 being 1.72 (± 0.71) and 1.92 (± 0.97) h, respectively ($P > 0.05$). The mean clarithromycin C_{max} of 0.76 (± 0.24) and 0.72 (± 0.25) mg/liter (formulations 1 and 2, respectively) and AUC_{0-24} of 4.21 (± 1.52) and 3.96 (± 1.55) mg/liter · h (formulations 1 and 2, respectively) were not significantly different between the two formulations ($P > 0.05$). The clarithromycin AUC_{0-24} ratio of formulation 1 versus 3 was 0.51 (Table 2), indicative of a 51% absolute bioavailability of parent compound for this formulation. However, when adjusted for potency (formulation 1, 98.4%; formulation 3, 106.6%), the absolute bioavailability of the parent compound from this formulation was 55%. Similar results were noted for formulation 2, with unadjusted and adjusted absolute bioavailabilities of parent compound being 47 and 52%, respectively.

After oral dosing with 250 mg of clarithromycin, 14-hydroxyclarithromycin was rapidly generated, with mean T_{max} for formulations 1, 2, and 3 of 2.17 (± 0.77), 2.32 (± 1.17), and 2.05 (± 0.62) h, respectively ($P > 0.05$). The mean

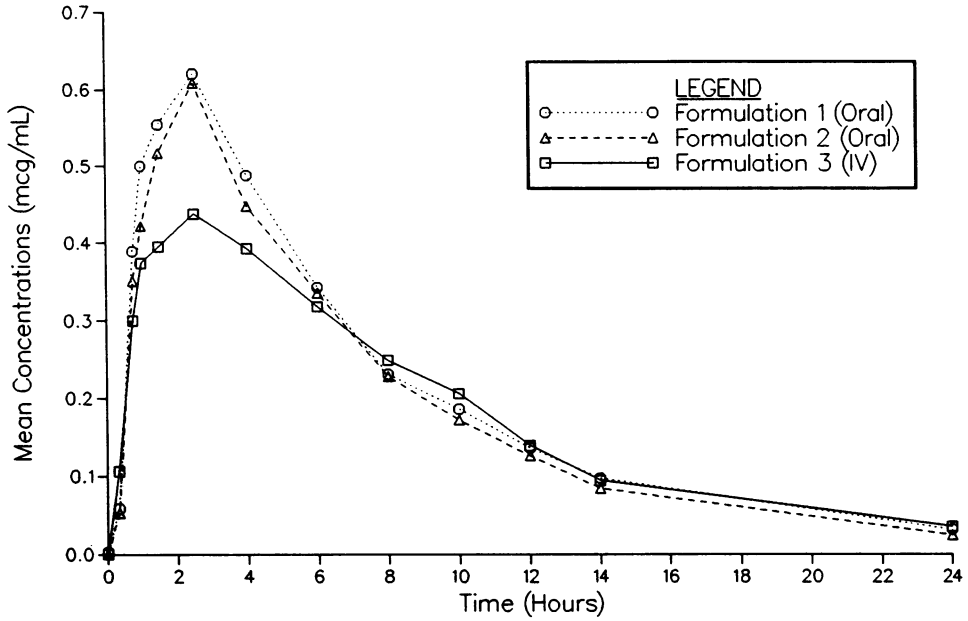

FIG. 2. Mean 14-hydroxyclarithromycin concentration-time profiles (in plasma) after oral and i.v. administration of 250 mg of clarithromycin. Standard deviation bars were omitted for purposes of clarity.

metabolite C_{max} of 0.65 (± 0.19) and 0.64 (± 0.20) mg/liter (formulations 1 and 2, respectively) and AUC_{0-24} of 4.91 (± 1.12) and 4.58 (± 1.16) mg · h/liter (formulations 1 and 2, respectively) were quite similar ($P > 0.05$). The C_{max} data of formulations 1 and 2 and the AUC_{0-24} of formulation 1 were significantly higher than those of formulation 3 [0.45 (± 0.080) mg/liter and 4.38 (± 0.99) mg · h/liter] ($P < 0.05$). The difference in AUC_{0-24} between formulations 2 and 3 was not statistically significant ($P > 0.05$). The metabolite AUC_{0-24} ratio of formulation 1 versus 3 adjusted for potency differences was 1.22, while a value of 1.15 was noted for formulation 2 versus 3.

For a drug cleared only through hepatic metabolism and renal excretion, the metabolite AUC after intraportal (i.p.) administration (100% absorption with first-pass metabolism) should always be greater than the metabolite AUC after i.v. administration of an equivalent dose (10). Under such assumptions, the ratio of metabolite AUC after i.p. versus i.v. administration can be estimated according to the following equation (11): $(AUC_m)_{i.p.}/(AUC_m)_{i.v.} = 1 + (CL_{R,D}/Q_{HV})$, where $CL_{R,D}$ is renal clearance of parent compound and Q_{HV} denotes total hepatic blood flow. By using a $CL_{R,D}$ of 129 ml/min (5) and 800 ml/min as the assumed hepatic plasma flow rate, an estimated ratio of 1.16 can be calculated. The observed ratios of 1.22 and 1.15 for formulations 1 and 2, respectively, would suggest nearly complete absorption and notable first-pass metabolism.

As discussed by Pang and Kwan (12), no precise estimation of fraction absorbed can be obtained from metabolite AUC data after oral and i.v. administration of parent drug

TABLE 1. Mean ± standard deviation (range) pharmacokinetic parameters for clarithromycin and 14-hydroxyclarithromycin after oral and i.v. administration of single 250-mg doses

Compound and formulation	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-24} (mg · h/liter)	$AUC_{0-\infty}$ (mg · h/liter)	$t_{1/2}$[a] (h)	CL (ml/min)	V (liters)
Clarithromycin							
Formulation 1	0.76 ± 0.24 (0.40–1.22)	1.72 ± 0.71 (0.75–2.50)	4.21 ± 1.52 (2.09–8.21)	4.27 ± 1.52 (2.09–8.21)	2.7 (1.8–6.5)	NA[b]	NA
Formulation 2	0.72 ± 0.25 (0.32–1.25)	1.92 ± 0.97 (0.75–4.00)	3.96 ± 1.55 (1.83–7.74)	4.03 ± 1.56 (1.83–7.74)	2.6 (1.6–9.5)	NA	NA
Formulation 3	2.78 ± 0.50 (2.10–3.81)	NA	8.41 ± 2.44 (4.78–14.61)	8.63 ± 2.62 (5.09–15.46)	2.8 (2.3–3.5)	519 ± 135 (269–819)	125 ± 27 (82–188)
14-Hydroxyclarithromycin							
Formulation 1	0.65 ± 0.19 (0.37–1.09)	2.17 ± 0.77 (0.75–4.00)	4.91 ± 1.12 (3.11–7.54)	4.91 ± 1.12 (3.11–7.54)	4.2 (2.7–10.1)	NA	NA
Formulation 2	0.64 ± 0.20 (0.18–1.07)	2.32 ± 1.17 (1.00–6.00)	4.58 ± 1.16 (2.48–6.58)	4.63 ± 1.17 (2.48–6.58)	3.9 (1.6–12.3)	NA	NA
Formulation 3	0.45 ± 0.08 (0.31–0.62)	2.05 ± 0.62 (1.00–2.50)	4.38 ± 0.99 (2.72–6.46)	4.44 ± 0.93 (2.72–6.46)	5.1 (2.7–8.3)	NA	NA

[a] Harmonic mean.
[b] NA, not applicable or available.

TABLE 2. Bioavailability analyses for clarithromycin and 14-hydroxyclarithromycin after oral and i.v. administration of single 250-mg doses

Compound and compared formulations	AUC (adjusted means)	Difference[a] in means (SE)	Ratio of adjusted means	90% CI[b] for ratio
Clarithromycin				
Formulation 1 versus 3	4.24 versus 8.39	−4.15 (0.324)	0.51	0.43–0.58
Formulation 2 versus 3	3.95 versus 8.39	−4.44 (0.324)	0.47	0.39–0.55
14-Hydroxyclarithromycin				
Formulation 1 versus 3	4.93 versus 4.37	0.56 (0.230)	1.13	1.02–1.23
Formulation 2 versus 3	4.59 versus 4.37	0.21 (0.230)	1.05	0.94–1.16

[a] Differences were calculated before rounding.
[b] CI, confidence interval.

alone. However, by using an average protein binding of 70%, erythrocyte-to-plasma concentration ratio of 0.2, and nonrenal clearance of about 0.3 liter/h/kg of body weight or 21.3 liter/h (for mean body weight of 71 kg) for clarithromycin on the basis of previous pharmacokinetic data (5) and by using the normal average values of 0.47 for hematocrit and 90 liter/h for hepatic blood flow, a reasonable extraction ratio (ER) could be estimated by the following equations (18): $CL_{b,int} = CL_b \div [F_b \cdot (1 - CL_b/Qh)]$ and $ER = F_b \cdot CL_{b,int} \div (Qh + F_b \cdot CL_{b,int})$, where intrinsic clearance ($CL_{b,int}$) was derived from the blood clearance (CL_b), free fraction in blood (F_b), and hepatic blood flow (Qh). The above assumptions yielded an extraction ratio of 0.38, with the corresponding estimated maximum bioavailability of 0.62. The fraction of dose absorbed is estimated to be 89% on the basis of the ratio of the observed (0.55) and the predicted (0.62) bioavailabilities. The pharmacokinetic analysis again suggests nearly complete absorption of the drug from the two oral formulations. Results from this study support the contentions that clarithromycin undergoes marked first-pass metabolism to the active 14-hydroxy metabolite and that the bioavailability of antimicrobial activity after oral administration is substantial.

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REFERENCES

1. **Akaike, H.** 1976. An information criterion (AIC). Math. Sci. **14**:5–9.
2. **Anderson, R., G. Joone, and E. J. von Rensburg.** 1988. An in-vitro evaluation of the cellular uptake and intraphagocytic bioactivity of clarithromycin (A-56268, TE-031), a new macrolide antimicrobial agent. J. Antimicrob. Chemother. **22**:923–933.
3. **Bryan, J. P., C. Waters, J. Sheffield, and K. F. Wagner.** 1990. In vitro activity of tosufloxacin (A-60969) and clarithromycin (A-56268, TE-031) against resistant Haemophilus influenzae, Streptococcus pneumoniae and Branhamella catarrhalis isolates. Eur. J. Clin. Microbiol. Infect. Dis. **9**:361–365.
4. **Chu, S.-Y., L. T. Sennello, and R. C. Sonders.** 1991. Simultaneous determinations of clarithromycin and 14(R)-hydroxyclarithromycin in plasma and urine using high performance liquid chromatography with electrochemical detection. J. Chromatogr. **571**:199–208.
5. **Ferrero, J. L., B. A. Bopp, K. C. Marsh, et al.** 1990. Metabolism and disposition of clarithromycin in man. Drug Metab. Dispos. **18**:441–446.
6. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed. Marcel Dekker, Inc., New York.
7. **Gorzynski, E. A., S. I. Gutman, and W. Allen.** 1989. Comparative antimycobacterial activities of difloxacin, temafloxacin, enoxacin, pefloxacin, reference fluoroquinolones, and a new macrolide, clarithromycin. Antimicrob. Agents Chemother. **33**: 591–592.
8. **Hardy, D. J., D. M. Hensey, J. M. Beyer, C. Vojtko, E. J. McDonald, and P. B. Fernandes.** 1988. Comparative in vitro activities of 14-, 15-, and 16-membered macrolides. Antimicrob. Agents Chemother. **32**:1710–1719.
9. **Hardy, D. J., R. N. Swanson, R. A. Rode, K. Marsh, N. L. Shipkowitz, and J. J. Clement.** 1990. Enhancement of the in vitro and in vivo activities of clarithromycin against *Haemophilus influenzae* by 14-hydroxyclarithromycin, its major metabolite in humans. Antimicrob. Agents Chemother. **34**:1407–1413.
10. **Klippert, P. J. M., and J. Noordhoek.** 1985. The area under the curve of metabolites for drugs and metabolites cleared by the liver and extrahepatic organs. Drug Metab. Dispos. **13**:97–101.
11. **Pang, K. S.** 1981. Metabolite pharmacokinetics: the area under the curve of metabolite and fractional rate of metabolism of a drug after different routes of administration for renally and hepatically cleared drugs and metabolites. J. Pharmacokinet. Biopharm. **9**:477–487.
12. **Pang, K. S., and K. C. Kwan.** 1983. A commentary: methods and assumptions in the kinetic estimation of metabolite formation. Drug Metab. Dispos. **11**:79–84.
13. **Perronne, C., A. Gikas, C. Truffot-Pernot, J. Grosset, J.-J. Pocidalo, and J. L. Vilde.** 1990. Activities of clarithromycin, sulfisoxazole, and rifabutin against *Mycobacterium avium* complex multiplication within human macrophages. Antimicrob. Agents Chemother. **34**:1508–1511.
14. **Rolston, K., G. Gooch, and D. Ho.** 1989. In vitro activity of clarithromycin (A-56268; TE-031) against gram-positive bacteria. J. Antimicrob. Chemother. **23**:455–457.
15. **SAS Institute Inc.** 1982. SAS user's guide. SAS Institute Inc., Cary, N.C.
16. **Sedman, A. J., and J. G. Wagner.** 1976. CSTRIP, a Fortran IV computer program for obtaining initial polyexponential parameter estimates. J. Pharm. Sci. **65**:1006–1010.
17. **Sefton, A. M., J. P. Maskell, F. J. Yong, C. Shu-Jing, and J. S. Williams.** 1988. Comparative in-vitro activity of A-56268. Eur. J. Clin. Microbiol. Infect. Dis. **7**:798–802.
18. **Wilkinson, G. R., and D. G. Shand.** 1975. A physiological approach to hepatic drug clearance. Clin. Pharmacol. Ther. **18**:380–390.