ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1992, p. 2447–2453
0066-4804/92/112447-07$02.00/0

Vol. 36, No. 11

Pharmacokinetics of Clarithromycin, a New Macrolide, after Single Ascending Oral Doses

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Received 22 May 1991/Accepted 8 September 1992

The pharmacokinetics and safety of single ascending doses of clarithromycin (6-O-methylerythromycin A) were assessed in a placebo-controlled, double-blind, randomized trial with 39 healthy male volunteers. Subjects were randomized to receive single doses of either placebo or 100, 200, 400, 600, 800, or 1,200 mg of clarithromycin. Blood and urine collections were performed over the 24 h following administration of the test preparation. Biological specimens were analyzed for clarithromycin and 14(*R*)-hydroxyclarithromycin content by a high-performance liquid chromatographic technique. The pharmacokinetics of clarithromycin appeared to be dose dependent, with terminal disposition half-life ranging from 2.3 to 6.0 h and mean ± standard deviation area under the concentration-versus-time curve from time 0 to infinity for plasma ranging from 1.67 ± 0.48 to 3.72 ± 1.26 mg/liter · h per 100-mg dose over the 100- to 1,200-mg dose range. Similar dose dependency was noted in the pharmacokinetics of the 14(*R*)-hydroxy metabolite. Mean urinary excretion of clarithromycin and its 14(*R*)-hydroxy metabolite ranged from 11.5 to 17.5% and 5.3 to 8.8% of the administered dose, respectively. Urinary excretion data and plasma metabolite/parent compound concentration ratio data suggested that capacity-limited formation of the active metabolite may account, at least in part, for the nonlinear pharmacokinetics of clarithromycin. No substantive dose-related trend was observed for the renal clearance of either compound. There were no clinically significant drug-related alterations in laboratory and nonlaboratory safety parameters. In addition, there was no significant difference between placebo and clarithromycin recipients in the incidence or severity of adverse events. Clarithromycin appears to be safe and well tolerated.

The new 14-membered macrolide antimicrobial agent clarithromycin (A-56268, TE-031) is active in vitro against several important gram-positive and gram-negative pathogens, such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus* species, *Legionella* species, *Mycobacterium avium* complex, and *Chlamydia* species (2, 4, 6, 8–10, 16, 19). Clarithromycin is active intracellularly, and its action is static or bactericidal, depending on the organism and antimicrobial agent concentration (2). Clarithromycin is more acid stable than erythromycin and in animal models achieves higher concentrations in plasma and tissue than erythromycin, especially in the lung (12, 13, 15). The Food and Drug Administration-approved dosage regimen for clarithromycin ranges from 250 to 500 mg twice daily (respiratory tract and skin or skin structure infections).

The present study was designed to assess the pharmacokinetics and safety of oral clarithromycin in a single-ascending-dose study in healthy young adult male volunteers.

(This work was presented in part at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., in 1986, abstract 419.)

MATERIALS AND METHODS

Subjects. Thirty-nine male volunteers, with a mean ± standard deviation (SD) age, weight, and height of 25.3 ± 4.0 (range, 19 to 36) years, 71.4 ± 9.8 (range, 55.9 to 96.9) kg, and 175 ± 7 (range, 158 to 191) cm, participated in the study. All were healthy as determined by medical history, physical examination, clinical laboratory studies, electrocardiography, and audiometry criteria. No subjects were receiving chronic medication.

The study was approved by the Institutional Review Board of Quincy Research Center, Kansas City, Mo., and all subjects provided written, informed consent prior to participation.

Study design. This study was single center, randomized, double blind, and placebo controlled in design. Target enrollment was 36 subjects, randomized into three groups of 12 subjects each. Within each group, eight subjects received clarithromycin while four subjects received placebo. Group I subjects were randomized to receive a single dose of either placebo or 200 mg of clarithromycin followed 21 days later by a randomization to receive either placebo or 800 mg of clarithromycin. Group II subjects were randomized to receive a single dose of either placebo or 400 mg of clarithromycin followed 21 days later by randomization to receive either placebo or 1,200 mg of clarithromycin. Group III subjects were randomized to receive a single dose of either placebo or 600 mg of clarithromycin followed 21 days later by randomization to receive either placebo or 100 mg of clarithromycin. Timing of the study groups was staggered so that administration of successively higher clarithromycin doses occurred only after the safety of the lower dose(s) had been established, except that the 100-mg-dose study was added later by protocol amendment to obtain additional pharmacokinetic information. All test doses were administered after an 8-h overnight fast with at least 200 ml of water. Food was prohibited until 4 h after test preparation administration. Water was ingested on at least an hourly basis over the first 12 h following test preparation administration to facilitate serial urine collections.

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Sample collection. Ten milliliters of blood was collected in heparinized tubes prior to and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 h following test preparation administration. After centrifugation, the resulting plasma samples were stored at −20°C until assayed.

Urine was collected over the following intervals: predose and 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, and 11 to 12 h following test preparation administration. Urine volumes were measured, and aliquots were stored at −20°C until assayed.

Biological specimens were collected from all study participants regardless of treatment randomization to maintain study blinding.

Analytical methodology. The concentrations of clarithromycin and 14(*R*)-hydroxyclarithromycin in plasma and urine were determined by a high-performance liquid chromatography method (5). In brief, plasma or urine samples were mixed with the internal standard (erythromycin A 9-0-methyloxime), alkalinized with sodium carbonate, and extracted with ethyl acetate-hexane (1:1). The organic phase was evaporated to dryness, and the residues were redissolved in acetonitrile, which was then injected into the chromatograph. The chromatograph consisted of a reverse-phase C-8 column (5-μm particle size, 4.6-mm inside diameter by 25 cm; Spherisorb; Phenomenex, Rancho Palo Verdes, Calif.) eluted with a mobile phase consisting of acetonitrile (48%, vol/vol), methanol (10%), 0.05 M acetic acid, and NaOH to produce a pH of 7.5. The effluent was monitored via electrochemical detection (model 5100 A detector; Environmental Sciences Associates, Bedford, Mass.) with the electric potentials of the screening and working electrodes set at +0.5 V and 0.78 ± 0.04 V, respectively. The within-day and between-day relative SDs for both compounds over the standard curve concentration ranges (0.05 to 4 mg/liter for plasma and 1 to 500 mg/liter for urine) were ≤8% (5).

Safety assessment. Vital signs were assessed at specified intervals over the 24-h period following test preparation administration, while clinical laboratory tests were conducted 24 h and 5 days after administration. Electrocardiography and audiometry were repeated on day 5 after administration.

Pharmacokinetic analysis. Concentration-versus-time data for both the parent compound and active 14(*R*)-hydroxy metabolite in plasma were subjected to curve stripping and sequential polyexponential regression analyses using CSTRIP and NONLIN (14, 18). A weighting by the reciprocal of concentration was used in the majority of data fits, although a weight of 1 in a few cases resulted in superior fidelity of fitting. The appropriate exponential model was judged by using the Akaike information criterion (1, 20). Parameters obtained from the model fitting included absorption, formation, and elimination (β) rate constants; lag time to absorption or metabolite formation; terminal disposition half-life ($t_{1/2\beta}$); peak concentration in plasma (C_{max}); time to C_{max}; area under the concentration-versus-time curve from time 0 to infinity for plasma ($AUC_{0-\infty}$); apparent total body clearance (CL_f); and apparent volume of distribution by standard techniques (7). In addition, percent urinary excretion over a 12-h period following dosing and renal clearance (CL_R) were measured by model-independent techniques (7).

Statistical analysis. All statistical analyses utilized the Statistical Analysis System procedures FREQ, CORR, and GLM (17). For each subject, each dose was considered an independent event, since 21 days elapsed between dose administrations and subjects were independently randomized prior to each of the two dose administrations. The total number of exposures was used as the denominator when calculating the incidence of adverse events, which were analyzed by Fisher's exact test. For pharmacokinetic parameters, the Bonferroni procedure was used for the comparison of dose groups with the mean square for error from the analysis of variance as the estimate of the variance. Also, Pearson's correlation coefficient between dose and the pharmacokinetic variables was obtained. Statistical significance was assessed at the 5% level. All data are expressed as mean ± SD except for $t_{1/2\beta}$ (harmonic mean).

RESULTS

Thirty-six subjects were originally enrolled in the protocol and assigned to the three study groups. Three replacement subjects were subsequently enrolled because subjects failed to report for the second dose administration (all for personal reasons). Thus, a total of 39 subjects participated. As discussed above in "Statistical analysis," the two dose administrations were considered independent, and thus, after randomization, the total number of observation in the study was 71:47 in the clarithromycin group and 24 in the placebo group.

Safety. No clinically significant drug-related trends were noted in medical history, physical examination, electrocardiographic, vital sign, audiometric, and clinical laboratory (hematology, chemistry, and urinalysis) assessments. Sixteen of 47 clarithromycin recipients (34%) and 4 of 24 placebo recipients (17%) experienced one or more adverse events (P = not significant). The most frequent event reported in the clarithromycin group was nausea (13%). All adverse events were mild to moderate in severity and self-limited.

Pharmacokinetics. Figures 1 and 2 illustrate the concentration-versus-time profiles of clarithromycin and 14(*R*)-hydroxyclarithromycin in plasma after ascending single oral doses of clarithromycin in the healthy study volunteers, respectively. Tables 1 and 2 illustrate the pharmacokinetic parameters of clarithromycin and 14(*R*)-hydroxyclarithromycin after ascending single oral doses of clarithromycin in the volunteers, respectively. Model-derived C_{max} and $AUC_{0-\infty}$ data agreed well with observed C_{max} and trapezoidally derived $AUC_{0-\infty}$, and thus, only model-derived data are presented in this report. Results from statistical comparison between dose groups for the pertinent pharmacokinetic parameters are also presented in Tables 1 and 2.

On the basis of the Akaike information criterion, a monoexponential elimination model, that is, a one-compartment open model, was found to most appropriately describe the plasma clarithromycin concentration-versus-time data. After oral administration, clarithromycin was rapidly absorbed, with C_{max} generally reached within 1.5 to 3 h following dosing. The mean C_{max} increased approximately in proportion to dose from 0.35 mg/liter (100-mg dose) to 3.97 mg/liter (1,200-mg dose). Significant dose dependency in clarithromycin pharmacokinetics was noted for β, CL_R, dose-normalized $AUC_{0-\infty}$, and CL_f data ($P < 0.05$) (Fig. 3). The decrease in CL_f with increasing dose and the corresponding increase of the dose-normalized $AUC_{0-\infty}$ are most likely due to the dose-dependent decrease in β (or increase in $t_{1/2\beta}$), because the apparent volume of distribution data, as shown in Table 1, show no apparent dose-related changes. This relatively constant apparent volume of distribution (a main determinant for C_{max}) across various doses may also explain the apparent dose linearity of C_{max}. The mean urinary recovery of the parent compound ranged from 11.5 to 17.5%

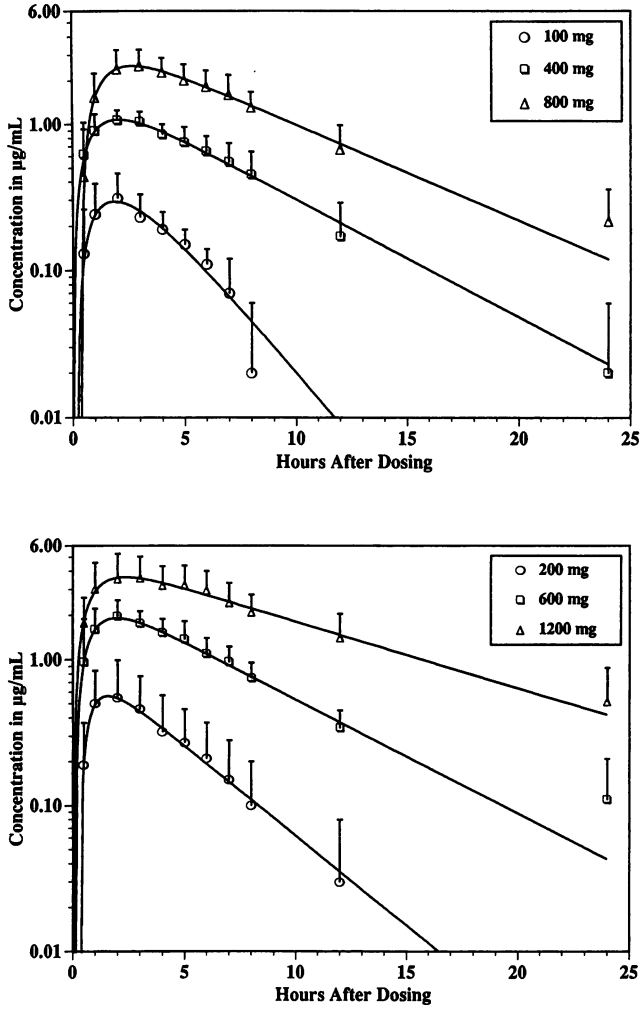

FIG. 1. Mean ± SD plasma clarithromycin concentration-versus-time profiles following oral administration of single doses of clarithromycin to healthy volunteers.

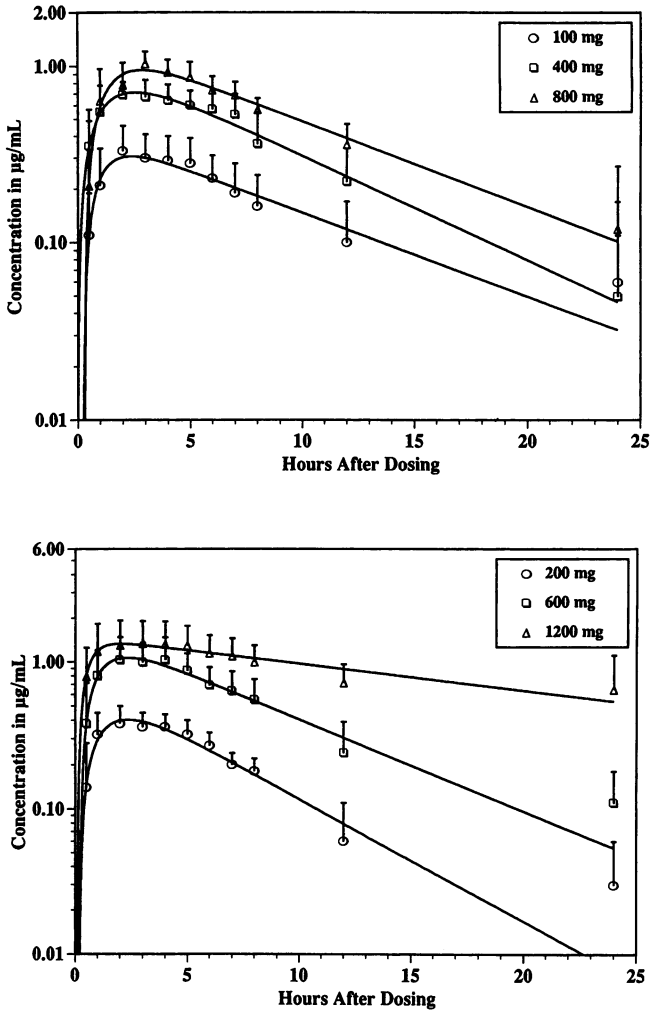

FIG. 2. Mean ± SD plasma 14(*R*)-hydroxyclarithromycin concentration-versus-time profiles following oral administration of single doses of clarithromycin to healthy volunteers.

of the administered dose over a 12-h time interval following dosing, while mean CL_R ranged from 97 to 198 ml/min across dose groups.

A monoexponential elimination model was also found to most appropriately describe the plasma 14(*R*)-hydroxy metabolite concentration-versus-time data. Similar to the parent compound, the observed metabolite $t_{1/2\beta}$ increased with increasing clarithromycin dose, from a mean of 2.4 h after 100 mg to 9.2 h after 1,200 mg (for β, $r = -0.37$ and $P < 0.05$). Across the 100- through 1,200-mg-dose groups, the mean ratio of metabolite to parent compound concentration in plasma was 0.81, ranging from a mean of 1.58 at the 100-mg dose level to a mean of 0.53 at the 1,200-mg dose level. This trend to decline with increasing dose is also reflected in the mean metabolite/parent $AUC_{0-\infty}$ ratios, which are illustrated in Table 2. Mean urinary recovery of the metabolite ranged from 5.3 to 8.8% of the administered dose over a 12-h interval following dosing, while mean CL_R ranged from 62 to 120 ml/min across dose groups. Correlation analysis of mean urinary recovery of the metabolite versus dose revealed a small but statistically significant downward trend with increasing dose. The mean metabolite/parent drug urinary excretion ratios were 0.81, 0.67, 0.63, 0.50, 0.42, and 0.41 for the 100-, 200-, 400-, 600-, 800-, and 1,200-mg groups, respectively, showing a very significant downward trend with increasing dose ($r = -0.60$) similar to the corresponding ratios of $AUC_{0-\infty}$.

DISCUSSION

The pharmacokinetics of clarithromycin and its 14(*R*)-hydroxy metabolite appear to be nonlinear. Nonlinearity in the pharmacokinetics of both compounds was suggested by the dose dependency noted in β, dose-normalized $AUC_{0-\infty}$, and CL_f. The significant decline in the metabolite/parent compound concentration in plasma ratio with increasing dose and the decline in urinary recovery of the metabolite with increasing dose were consistent with a capacity-limited metabolism of the parent compound to the 14(*R*)-hydroxy metabolite. This may account, at least in part, for the nonlinearity of clarithromycin pharmacokinetics. Similar nonlinear pharmacokinetics have been noted for the macrolide erythromycin (3, 10). CL_Rs of both the parent drug and the metabolite showed statistically significant differences between some dose groups, very possibly due to the different subjects used in each group, because further correlation

TABLE 1. Pharmacokinetic parameters of clarithromycin after single-oral-dose administration of various doses of clarithromycin[a]

Dose group (n)	Mean ± SD (range)										
	k_a (h^{-1})	$t_{lag\ a}$ (h)	C_{max} (mg/liter)	t_{max} (h)	β (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg/liter · h)	CL_f (ml/min)	V (liters)	F_e (%)	CL_R (ml/min)
100 mg (6)	2.26 ± 1.16 (1.07–4.30)	0.34 ± 0.36 (0.00–1.00)	0.35 ± 0.10 (0.26–0.52)	1.46 ± 0.41 (0.72–1.93)	0.31 ± 0.05 (0.23–0.36)	2.27 (1.91–2.97)	1.67 ± 0.48 (1.23–2.51)	1,060 ± 258 (665–1,360)	218 ± 79 (110–330)	11.5 ± 3.3 (8.0–17.4)	126 ± 14 (114–146)
200 mg (8)	3.75 ± 5.27 (0.61–16.39)	0.34 ± 0.17 (0.00–0.50)	0.60 ± 0.43 (0.14–1.42)	1.56 ± 0.49 (0.69–2.20)	0.30 ± 0.13 (0.18–0.57)	2.33 (1.21–3.91)	2.99 ± 1.97 (1.02–6.54)	1,645 ± 1,039 (509–3,278)	386 ± 332 (96–1,109)	13.9 ± 8.0 (7.4–31.1)	198 ± 98 (74–394)
400 mg (8)	1.67 ± 1.11 (0.71–4.03)	0.16 ± 0.23 (0.00–0.64)	1.13 ± 0.18 (0.95–1.53)	1.86 ± 0.72 (0.81–3.09)	0.19 ± 0.05 (0.14–0.29)	3.60 (2.36–5.06)	8.55 ± 2.35 (6.10–11.96)	829 ± 209 (562–1,092)	261 ± 51 (219–367)	13.6 ± 3.8 (8.1–20.9)	125 ± 31 (80–168)
600 mg (8)	1.95 ± 1.35 (0.70–4.52)	0.23 ± 0.17 (0.00–0.46)	2.03 ± 0.59 (1.41–3.07)	1.83 ± 0.65 (0.75–2.50)	0.19 ± 0.07 (0.12–0.28)	3.64 (2.51–5.88)	15.44 ± 4.18 (9.44–20.08)	699 ± 219 (498–1,059)	230 ± 58 (132–306)	17.5 ± 3.6 (9.8–21.5)	140 ± 44 (94–212)
800 mg (8)	1.18 ± 0.76 (0.54–2.93)	0.43 ± 0.25 (0.00–0.90)	2.63 ± 0.72 (1.85–3.78)	2.67 ± 0.77 (1.60–3.99)	0.16 ± 0.05 (0.08–0.22)	4.25 (3.12–9.25)	24.73 ± 7.67 (16.40–38.71)	583 ± 167 (344–813)	232 ± 79 (124–327)	16.8 ± 4.9 (13.0–27.7)	117 ± 20 (84–140)
1,200 mg (8)	4.43 ± 6.36 (0.61–18.79)	0.40 ± 0.59 (0.00–1.80)	3.97 ± 1.40 (1.55–5.64)	2.20 ± 1.15 (0.72–3.67)	0.12 ± 0.04 (0.05–0.17)	5.98 (4.03–14.04)	44.60 ± 15.10 (24.13–72.98)	496 ± 173 (274–829)	301 ± 198 (131–762)	13.3 ± 2.2 (9.9–16.5)	97 ± 40 (47–173)
Statistical comparisons[b]	800 400 600 100 200 1,200		400[c] 200 800 1,200 600 100		1,200 800 600 400 200 100		200[c] 100 400 600 800 1,200	1,200 800 600 400 100 200	100 600 800 400 1,200 200	100 1,200 400 200 800 600	1,200 800 400 100 600 200

[a] k_a, absorption rate constant; $t_{lag\ a}$, lag time to absorption; t_{max}, time to C_{max}; V, apparent volume of distribution; F_e, urinary excretion over a 12-h period following dosing. Other abbreviations are defined in the text.

[b] Dose groups (e.g., 800 = 800-mg group) are listed in order from lowest to highest group mean parameter value; values for bracketed dose groups are not significantly different.

[c] Dose-normalized data were used for comparison.

TABLE 2. Pharmacokinetic parameters of 14(*R*)-hydroxyclarithromycin after single-oral-dose administration of various doses of clarithromycin[a]

Dose group (*n*)	Mean ± SD (range)									
	k_f (h^{-1})	$t_{lag\ f}$ (h)	C_{max} (mg/liter)	t_{max} (h)	β (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg/liter · h)	F_e (%)	CL_R (ml/min)	Metabolite/ parent $AUC_{0-\infty}$ ratio
100 mg (6)	1.58 ± 1.16 (0.24–3.62)	0.39 ± 0.35 (0.00–1.00)	0.35 ± 0.13 (0.21–0.53)	2.09 ± 0.51 (1.52–2.89)	0.29 ± 0.34 (0.10–0.99)	2.40 (0.70–6.68)	3.06 ± 1.53 (1.90–6.01)	8.8 ± 2.5 (6.6–14.1)	62 ± 17 (39–82)	1.96 ± 1.13 (1.15–3.98)
200 mg (8)	1.26 ± 0.87 (0.43–2.78)	0.23 ± 0.21 (0.00–0.50)	0.41 ± 0.12 (0.25–0.63)	2.29 ± 0.53 (1.44–2.82)	0.21 ± 0.10 (0.10–0.41)	3.37 (1.68–7.02)	3.40 ± 0.87 (2.50–4.88)	7.7 ± 1.2 (6.5–10.1)	91 ± 23 (65–130)	1.56 ± 0.86 (0.59–3.07)
400 mg (6)	1.36 ± 0.72 (0.40–1.99)	0.14 ± 0.22 (0.00–0.55)	0.78 ± 0.21 (0.43–1.07)	2.11 ± 0.63 (1.53–3.06)	0.18 ± 0.12 (0.08–0.40)	3.89 (1.75–9.24)	7.52 ± 2.16 (4.75–10.66)	8.3 ± 2.0 (6.2–12.5)	100 ± 33 (79–158)	0.89 ± 0.25 (0.50–1.24)
600 mg (8)	1.27 ± 0.70 (0.40–2.35)	0.36 ± 0.37 (0.00–1.18)	1.06 ± 0.38 (0.64–1.84)	2.45 ± 0.90 (1.55–3.83)	0.18 ± 0.10 (0.09–0.40)	3.84 (1.74–7.35)	9.95 ± 3.33 (4.42–13.67)	8.6 ± 2.0 (5.5–11.4)	121 ± 50 (62–208)	0.68 ± 0.24 (0.24–1.12)
800 mg (7)	1.08 ± 0.41 (0.59–1.84)	0.38 ± 0.28 (0.00–0.84)	1.02 ± 0.22 (0.67–1.29)	2.72 ± 0.60 (1.96–3.47)	0.14 ± 0.04 (0.09–0.19)	5.09 (3.69–7.55)	10.70 ± 2.49 (6.91–14.17)	7.0 ± 2.3 (3.7–9.8)	120 ± 42 (54–182)	0.49 ± 0.14 (0.31–0.67)
1,200 mg (6)	1.56 ± 0.83 (0.55–2.67)	0.21 ± 0.32 (0.00–0.84)	1.54 ± 0.66 (0.85–2.66)	2.61 ± 1.36 (1.51–5.25)	0.08 ± 0.01 (0.06–0.09)	9.19 (7.43–12.17)	23.90 ± 7.06 (16.00–34.82)	5.3 ± 1.8 (2.9–8.7)	80 ± 26 (53–120)	0.55 ± 0.22 (0.22–0.81)
Statistical comparisons[b]	800 200 600 400 1,200 100		800[c] 1,200 600 400 200 100		1,200 800 600 400 200 100		800[c] 600 200 400 1,200 100	1,200 800 200 400 600 100	100 1,200 200 400 800 600	800 1,200 600 400 200 100

[a] k_f, formation rate constant; $t_{lag\ f}$, lag time to metabolite formation; t_{max}, time to C_{max}; F_e, urinary excretion over a 12-h period following dosing. Other abbreviations are defined in the text.
[b] Dose groups (e.g., 800 = 800-mg group) are listed in order from highest to lowest group mean parameter; values for bracketed dose groups are not significantly different.
[c] Dose-normalized data were used for comparison.

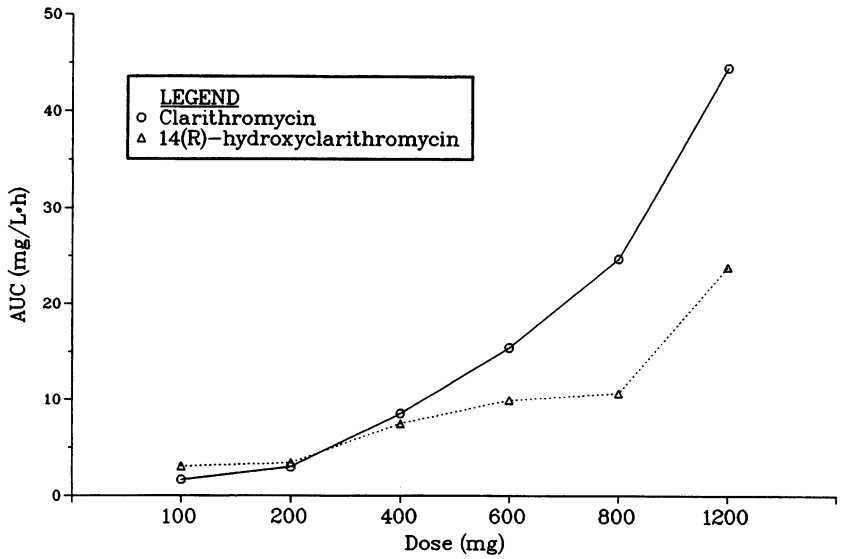

FIG. 3. Mean $AUC_{0-\infty}$ for clarithromycin and 14(*R*)-hydroxyclarithromycin versus clarithromycin dose following single-dose administration to healthy volunteers.

analysis revealed no dose-related trend for the CL_R of the metabolite. Although CL_R for the parent drug showed a significant dose-related trend, the correlation was weak ($r = -0.38$) and the trend was not substantive (regression slope of -0.058 with an intercept of 167.7). Thus for all practical purposes, renal elimination of both compounds appears to follow first-order kinetics. Oral bioavailability of clarithromycin does not appear to be dose dependent on the basis of urinary excretion data.

As discussed above, the disposition kinetics for clarithromycin are somewhat nonlinear. Furthermore, CL_R, which is a relatively important route for clarithromycin (in contrast to erythromycin), shows no apparent dose dependency. Thus, the actual disposition kinetics for clarithromycin are more complicated than would be suggested by the model used. The present model represents an approximation that allows reasonable description of the profiles at each dose but has its limitation with respect to dose extrapolation. The current data are, however, insufficient for precise estimations of parameters from test models which include both capacity-limited metabolism and a parallel first-order renal elimination.

Clarithromycin appeared to be safe and well tolerated in single doses as high as 1,200 mg. This would suggest that further multiple-dose pharmacokinetic and clinical trials with this compound are warranted.

ACKNOWLEDGMENTS

We thank Charles Locke for his valuable input in statistical interpretation and Mary F. Trkla for her expert secretarial assistance.

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