

Safety, Toleration, and Pharmacokinetics of Intravenous Azithromycin

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To date, the clinical pharmacology of large intravenous doses of azithromycin has not been described. In the present study, single 2-h intravenous infusions of 1, 2, and 4 g of azithromycin were administered to three parallel groups (in each group, six received active drug and two received placebo) of healthy male subjects. Toleration (assessed by scores of subject-administered visual analog scale tests spanning 0 [good] to 10 [poor]), safety, pharmacokinetics, and serum motilin levels were monitored for up to 240 h after the start of each intravenous infusion. Mean nausea scores of 0.0, 0.0, 1.0, and 0.5 and abdominal cramping scores of 0.0, 0.0, 0.4, and 0.4 for 12-h periods after doses of 0, 1, 2, and 4 g of azithromycin, respectively, suggested that azithromycin was well tolerated. Because of the standardized 1-mg/ml infusates, all subjects in the 4-g dosing group complained of an urgent need to urinate. There were no consistent trends in endogenous motilin levels throughout the study. The maximum concentration of azithromycin in serum (10 µg/ml after a 4-g dose) and the area under the concentration-time curve (82 µg · h/ml after a 4-g dose) were dose related. The mean pharmacokinetic parameters were an elimination half-life of 69 h, total systemic clearance of 10 ml/min/kg, and a volume of distribution at steady state of 33.3 liters/kg. The pharmacokinetic results suggest that the long half-life of azithromycin is due to extensive uptake and slow release of the drug from tissues rather than an inability to clear the drug. Single intravenous doses of up to 4 g of azithromycin in healthy subjects are generally well tolerated, and quantifiable concentrations may persist in serum for 10 days or more.

Azithromycin belongs to a new class of antibiotics known as the azalides. Although somewhat structurally similar to the macrolides (e.g., erythromycin), azithromycin has superior activity against gram-negative organisms while retaining good activity against gram-positive microorganisms (17, 19). Moreover, azithromycin differs from the classical macrolides, exhibiting a longer elimination half-life ($t_{1/2}$) and better tissue distribution (5). In contrast to the typical 10- and 14-day courses of antibiotics three or four times daily, azithromycin is given orally in single daily doses for 3 to 5 days for the treatment of most community-acquired infections.

Azithromycin is undergoing clinical trials for the treatment of human immunodeficiency virus-related diseases, such as *Mycobacterium avium* complex (1, 9, 10) and cryptosporidiosis (6). In many cases, azithromycin must be given intravenously because of the underlying enteropathies, which may limit oral drug absorption. Daily intravenous doses of up to 2 g are being studied with patients with cryptosporidiosis. Data on the safety and pharmacokinetics of intravenous azithromycin are required to support its use in patients requiring these large doses.

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MATERIALS AND METHODS

Study population and design. This double-blind, placebo-controlled, randomized, parallel-group study was conducted at the Clinical Pharmacology Unit at the National Medical Research Corporation, Hartford, Conn., and was approved by the Nutmeg Institutional Review Board. All subjects provided informed consent before participating in the study.

Three groups of eight subjects each were randomly assigned to receive active drug or placebo. Within each group, six subjects were assigned to active drug and two subjects were randomized to placebo (drug-free physiologic normal saline). Subjects were determined to be in good health by physical examination (including screening audiometry) and clinical laboratory tests, including a stool sample

test for ova, parasites, and *Clostridium difficile* toxin. Subjects were restricted from all standard prescription and nonprescription drugs for 2 weeks prior to participation and throughout the study period. Subjects also abstained from alcohol and caffeine-containing products for 3 days prior to and throughout the study.

Dosing started with the 1-g azithromycin group, followed at 2-day intervals with the 2- and 4-g dosing groups, the dose escalation being indexed to safety and toleration. Drug was prepared in sterile normal saline immediately prior to infusion and was infused with precalibrated infusion pumps over 2-h periods. Reconstituted active drug was clear and colorless and matched the drug-free placebo solution. Given the large volume of the highest-dose infusate (4 liters), two pumps were used for each subject in this group, one for infusion into each arm. Vital signs were determined and telemetry, electrocardiograms, assessments of side effects, and laboratory tests were carried out throughout and following the 2-h infusions. Each subject rated his gastrointestinal complaints (abdominal pain, nausea, "butterflies," urgent need to defecate, flatulence, regurgitation, hunger, heartburn, abdominal cramping, and burping or belching) on visual analog scales prior to the 2-h infusion, at 15, 30, 45, 60, and 90 min during the infusion, and at 2 (immediately after infusion), 4, 8, 12, 18, 24, 48, 72, 96, 144, 192, and 240 h after the start of the infusion. Blood samples sufficient to provide 3 ml of serum were collected prior to each visual analog scale rating throughout the 10-day study period for analysis of azithromycin. Blood samples obtained for the first 24 h were also analyzed for motilin levels by radioimmunoassay (Roche Biomedical Laboratories, Raritan, N.J.).

Pharmacokinetic analysis. Concentrations of azithromycin in serum were determined by high-performance liquid chromatography with electrochemical detection (15). Serum standards in the range of 0.010 to 1.20 µg/ml were prepared. Samples with concentrations greater than 1.20 µg/ml were diluted with control serum and reanalyzed. Standard curves were linear, with correlation coefficients greater than 0.994; the linear range of the assay was from 10 ng/ml to 1.21 µg/ml. Quadruplicate assays of standards produced relative standard deviations of <11%. For the duplicate quality control samples, the range of the error of the mean concentrations for nine assay runs was -2 to +10%. The mean error of seven duplicate sample concentrations for the standard curves differed from nominal concentrations by <10%. The lower limit of quantitation of the assay was 0.010 µg/ml; values below this were reported as 0.000 µg/ml.

The peak concentration and the corresponding time (T_{max}) were determined by observation of the serum concentration-time profile for each subject. The terminal elimination rate constant (k_{el}) was estimated by least-squares regression of the log-linear terminal portion of the concentration-time curve. The mean terminal $t_{1/2}$ was calculated as $\log 2/\text{mean } k_{el}$. The area under the serum concentration-time curve for the sampling period ($AUC_{0-\text{last}}$), where "last" represented the time of last measurable concentration, was estimated by trapezoidal summation. The $AUC_{0-\infty}$ was calculated as $AUC_{0-\text{last}} + C_{\text{last}}^*/k_{el}$, where C_{last}^* was the concentration estimated at the time of the last quantifiable concentration of drug from the aforementioned least-squares regression of the log-linear terminal portion of the concentration-time profile.

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TABLE 1. Side effects during the 2-h infusion period in healthy male subjects given various doses of azithromycin or placebo

Symptom	Difference from baseline visual analog score (mean \pm SD) for subjects ^a receiving:			
	Placebo	Single-dose azithromycin (g)		
		1	2	4
Abdominal pain	-0.33 \pm 0.24	0.25 \pm 0.17	0.86 \pm 0.36	1.37 \pm 0.77
Nausea	-0.17 \pm 0.08	0.00 \pm 0.00	1.61 \pm 0.79	1.07 \pm 0.74
Butterflies	-0.17 \pm 0.08	-0.25 \pm 0.09	-0.11 \pm 0.23	-0.80 \pm 0.55
Urgent need to defecate	-0.17 \pm 0.08	0.00 \pm 0.00	-0.14 \pm 0.07	-0.60 \pm 0.00
Flatulence	0.00 \pm 0.00	0.03 \pm 0.25	-0.08 \pm 0.14	-0.37 \pm 0.23
Regurgitation	-0.17 \pm 0.08	0.00 \pm 0.00	0.06 \pm 0.14	0.07 \pm 0.45
Hunger	1.53 \pm 0.60	2.42 \pm 1.03	1.42 \pm 0.57	-0.30 \pm 0.85
Heartburn	-0.17 \pm 0.08	0.06 \pm 0.09	0.50 \pm 0.24	-0.03 \pm 0.23
Abdominal cramping	-0.03 \pm 0.20	0.03 \pm 0.07	0.61 \pm 0.31	0.83 \pm 0.70
Burping or belching	-0.17 \pm 0.08	0.11 \pm 0.14	0.25 \pm 0.27	-0.10 \pm 0.21

^a Six subjects received 1 g of azithromycin, six received 2 g, five received 4 g, and six received placebo.

Total clearance (CL_t) was calculated by the ratio of dose to $AUC_{0-\infty}$. The volume of distribution at steady state (V_{ss}) was calculated by the equation $V_{ss} = \text{dose} \cdot AUMC_{0-\infty} / (AUC_{0-\infty})^2 - T \cdot \text{dose} / 2 \cdot AUC_{0-\infty}$, where AUMC was the area under the first moment of the serum concentration-time curve and T was the time of infusion (2 h). The $AUMC_{0-\text{last}}$ was estimated by trapezoidal summation and extrapolated to infinity by the equation $AUMC_{0-\infty} = AUMC_{0-\text{last}} + t_{\text{last}} \cdot C_{\text{last}} / k_{\text{el}} + C_{\text{last}} / k_{\text{el}}^2$, where t_{last} is the time of the last quantifiable concentration of drug.

Visual analog data analysis. Results of the rating on visual analog scales were summarized in two ways. The percentages of nonzero responses for each treatment group at each time point were calculated and plotted. The differences from baseline values of each symptom recorded on the visual analog scales were also plotted against time following the start of each intravenous infusion. Average values over the infusion period and the 12-h period following the start of the infusion were calculated and compared between treatment groups. No statistical analysis was applied to the mean scores. Changes in baseline gastrointestinal scores and serum motilin levels were analyzed by linear regression.

RESULTS

Safety and toleration data. A total of 23 healthy male volunteers (mean age, 26 years; age range, 18 to 43 years; mean weight, 76 kg; weight range, 64 to 91 kg) completed the study. One subject in the highest-dose group had a dosing error and received only 3 liters of infusate (=3 g of azithromycin); these data are not included in the summaries.

Treatment-related side effects were experienced by no subjects in the 1-g dosing group, by four of six subjects administered 2 g, and by all five subjects given 4 g of azithromycin. One of the six subjects given placebo had treatment-related side effects. Most side effects were gastrointestinal, and all were

mild. The most frequently reported side effects were nausea, tinnitus, and emesis. Four of the six subjects administered 2 g of azithromycin had neutropenia that was considered possibly related to treatment, with the most divergent absolute neutrophil counts ranging from 1,323 to 672 cells per mm^3 (normal range, 1,845 to 7,828 cells per mm^3). One of these subjects also had an increased eosinophil count (672 cells per mm^3 ; normal range, 0 to 412 cells per mm^3). Additionally, one subject given placebo had a decreased neutrophil count (1,023 cells per mm^3). Neutrophil abnormalities were not observed in the 1- or 4-g group.

There were no trends or consistent differences in vital signs among treatment groups. Four subjects in the highest-dose group (three receiving active drug and one receiving placebo) experienced transient increases in diastolic blood pressure during the infusions. The increase was quickly reversed after urination and was attributed to the large volume of fluid (4 liters) being infused. There were no arrhythmias detected by continuous telemetry or 12-lead electrocardiograms during or following the infusions of either azithromycin or placebo.

Visual analog data. The mean differences from baseline visual analog scores for each treatment group during the 2-h infusion and over the 12-h period following the start of each intravenous infusion are listed in Tables 1 and 2, respectively. For the abdominal pain scale, the percentage of nonzero values was highest in the group receiving 4 g of azithromycin (80% at the end of infusion). Consistent with this finding, the

TABLE 2. Side effects for the 12-h period after start of the 2-h infusion in healthy male subjects given various doses of azithromycin or placebo

Symptom	Difference from baseline visual analog score (mean \pm SD) for subjects ^a receiving:			
	Placebo	Single-dose azithromycin (g)		
		1	2	4
Abdominal pain	0.40 \pm 0.26	0.17 \pm 0.19	0.61 \pm 0.47	0.84 \pm 0.99
Nausea	-0.44 \pm 0.22	0.00 \pm 0.00	1.02 \pm 1.10	0.51 \pm 1.02
Butterflies	-0.11 \pm 0.11	-0.28 \pm 0.08	-0.19 \pm 0.21	-1.18 \pm 0.72
Urgent need to defecate	0.02 \pm 0.34	0.00 \pm 0.00	-0.15 \pm 0.06	-0.53 \pm 0.14
Flatulence	-0.11 \pm 0.11	0.19 \pm 0.35	-0.11 \pm 0.12	-0.36 \pm 0.22
Regurgitation	-0.11 \pm 0.11	0.00 \pm 0.00	0.04 \pm 0.11	-0.19 \pm 0.43
Hunger	0.91 \pm 1.71	1.43 \pm 2.19	0.89 \pm 1.78	-0.91 \pm 1.91
Heartburn	-0.11 \pm 0.11	0.04 \pm 0.07	0.33 \pm 0.31	-0.16 \pm 0.26
Abdominal cramping	-0.02 \pm 0.16	0.02 \pm 0.06	0.41 \pm 0.39	0.36 \pm 0.91
Burping or belching	-0.11 \pm 0.11	0.19 \pm 0.15	0.17 \pm 0.25	-0.33 \pm 0.40

^a Six subjects received 1 g of azithromycin, six received 2 g, five received 4 g, and six received placebo.

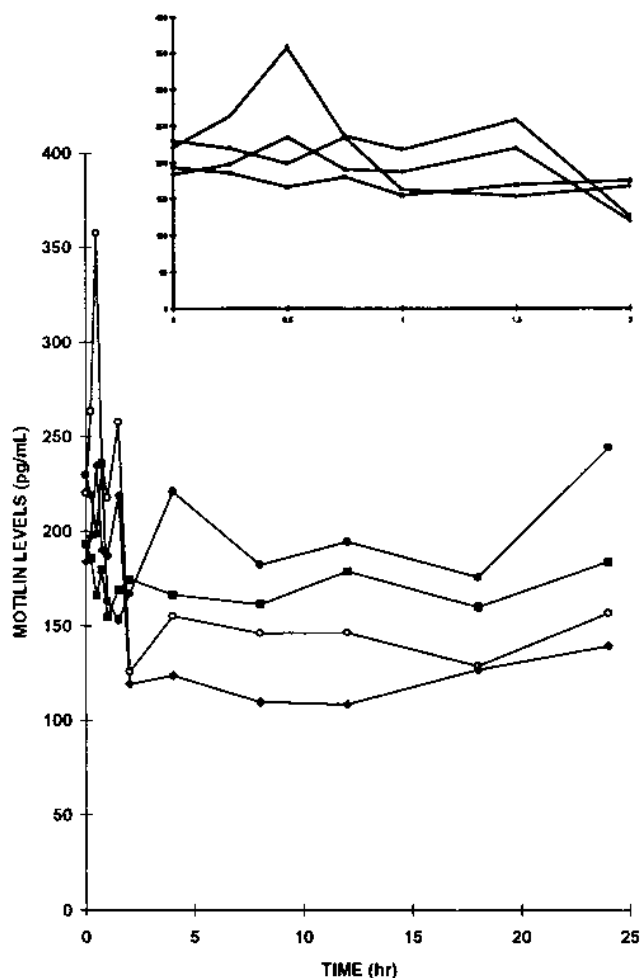


FIG. 1. Mean serum motilin concentration-time profiles after 2-h intravenous infusions of 1 (■), 2 (◆), and 4 (●) g of azithromycin or placebo (○) to healthy male subjects. (Inset) Mean motilin concentrations during 2-h infusions.

mean values for the 4-g group were generally higher during the infusion period. For nausea, the nonzero values during the last hour of infusion were 67% for the 2-g group and 60% for the 4-g group. Mean values of nausea were generally higher for these two groups than for those receiving placebo or for the 1-g group. Abdominal cramping was also seen most frequently in the 4-g group and was reflected in the mean value profile. No other symptoms appeared to be dose related.

Hunger was assessed as a reliability index for the subject-rated scales. As expected from the extensive fasting period prior to and during drug treatment (16 h), all subjects rated hunger high at baseline on the visual analog scales. Immediately following the noon meal, all subjects rated hunger very low, supporting subject compliance with the visual analog-scale test. Further, those subjects in the 4-g group reporting nausea and/or abdominal cramping rated hunger lower than the other groups during the infusions.

Motilin data. Mean serum motilin concentration-time profiles after administration of 1, 2, and 4 g of azithromycin or placebo are shown in Fig. 1. There were no apparent trends, patterns, or consistent changes in serum motilin concentrations among all treatment groups. The only observation of note is that one placebo subject had unusually high motilin levels during the intravenous infusion. No dose-dependent trends

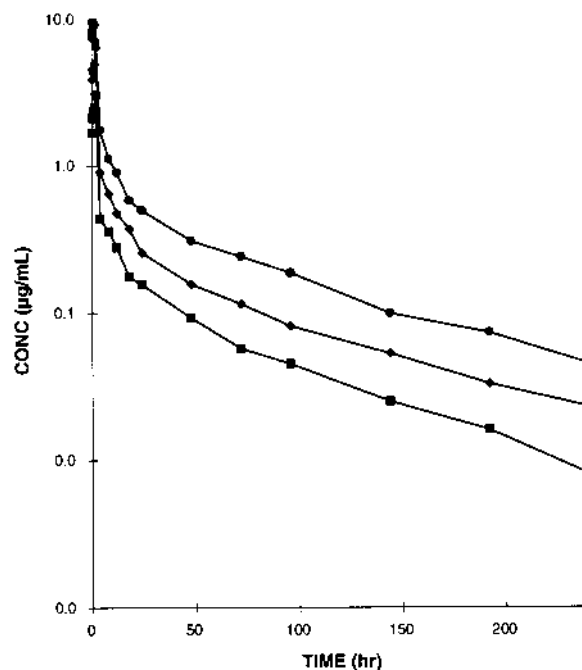


FIG. 2. Mean serum azithromycin concentration-time profiles after 2-h intravenous infusions of 1 (■), 2 (◆), and 4 (●) g of azithromycin to healthy male subjects.

were found. There was no association between motilin levels and subject-rated gastrointestinal symptoms in any treatment group.

Pharmacokinetic data. The mean serum azithromycin concentration-time profiles after administration of 1, 2, and 4 g of azithromycin are shown in Fig. 2 and 3. The mean azithromycin pharmacokinetic parameters are summarized in Table 3. Drug was still detected for 192 h in sera of all subjects given 1 g of azithromycin and for 240 h in sera of all subjects given 2 or 4 g of azithromycin. The T_{max} s closely approximated the end of the infusion period in all subjects given 1 or 2 g of azithromycin; however, the mean T_{max} following the 4-g dose was 1.05 h (range, 0.75 to 1.5 h). The mean $t_{1/2}$ s (in hours) were 64.8 (range, 49.6 to 84.1), 72.2 (range, 59.8 to 88.9), and 69.3 (range, 60.3 to 92.0) following doses of 1, 2, and 4 g of azithromycin, respectively. The mean CL_t (in milliliters per minute per kilogram) were 10.1 (range, 8.9 to 11.4), 9.5 (range, 7.9 to 11.1), and 11.0 (range, 8.3 to 13.5) following doses of 1, 2, and 4 g of azithromycin, respectively. The mean CL_t for all subjects was 10.2 ml/min/kg. The mean V_{ss} s (in liters per kilogram) were 30.1 (range, 24.0 to 36.0), 30.5 (range, 22.6 to 41.2), and 38.3 (range, 32.9 to 44.7) following doses of 1, 2, and 4 g of azithromycin, respectively. The mean V_{ss} for all subjects was 33.3 liters/kg. The $t_{1/2}$, CL_t , and V_{ss} for the subject who received 3 g were consistent with those of other subjects.

DISCUSSION

In this study, we explored the clinical pharmacology of single doses of azithromycin given intravenously in an attempt to define the maximum tolerated dose in healthy volunteers. Although the largest dose studied (4 g) was associated with the highest incidence of subject-rated symptoms, all symptoms were mild.

The most frequently reported gastrointestinal complaints were abdominal cramping and nausea. Even at the very high

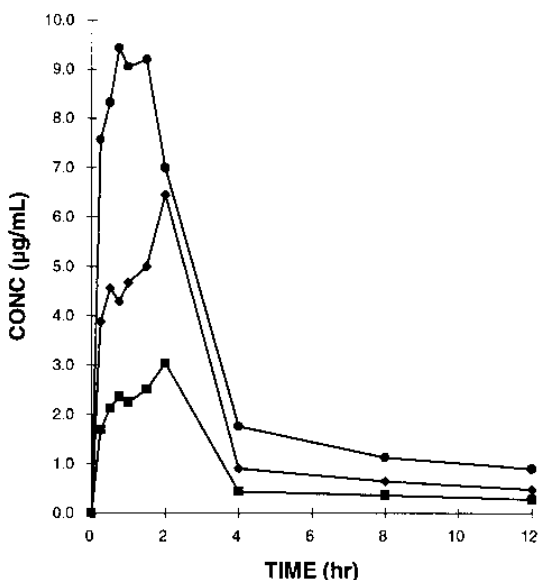


FIG. 3. Mean serum azithromycin concentration-time profiles for the first 12 h after the start of a 2-h intravenous infusion of 1 (■), 2 (◆), and 4 (●) g of azithromycin to healthy male subjects.

dose of 4 g (which is estimated to be 20 times the oral loading dose recommended on the basis of bioavailability), none of the gastrointestinal complaints required discontinuation of the study. Tinnitus was reported for two and three of the subjects given 2 and 4 g of azithromycin, respectively; it was mild and lasted less than 6 h. The principal investigator did not consider repeat audiometric examinations necessary for these subjects. Neutropenia was found in some patients given the 2-g azithromycin dose but not in the highest-dose group. Moreover, one subject administered placebo on the same day as those given 2 g of azithromycin had neutropenia. Thus, the finding of neutropenia is more likely to be laboratory error than a study-related event. Subsequent neutrophil counts for these subjects were normal.

Intravenous administration of macrolides has been associated with injection site pain, erythema, and swelling; these adverse events appear to be related both to infusate concentration and to rate of infusion. For these reasons, the active and placebo infusions were maintained at the same concentration of the active compound and duration among groups. No evidence of irritation was found in any subjects administered either active drug or placebo in this study.

Motilin is a 22-amino-acid gastrointestinal peptide that was first isolated from porcine duodenal mucosa. Cyclical changes in plasma motilin levels have been observed in fasting subjects and were found to be related to the interdigestive motor activity of the duodenum (14, 18). Duodenal acidification and fat ingestion have been shown to increase endogenous motilin release in human volunteers, thereby increasing contractile activity in the antrum and duodenum (12). The contractions may lead to diarrhea and abdominal cramping.

Erythromycin has been shown to mimic exogenous motilin in both animal and clinical models. The contractions in the stomach and duodenum produced by erythromycin were similar to naturally occurring activity in frequency, force, and duration (8, 16). In vitro studies have shown erythromycin to be a motilin receptor agonist. Whether the ensuing contractions are a result of direct action on the motilin receptor or whether the effect is due to release of endogenous motilin (13) remains

TABLE 3. Pharmacokinetic parameters after single intravenous doses of azithromycin in healthy male subjects

Parameter ^b (unit)	Value (mean ± SD) for subjects ^a receiving single-dose intravenous azithromycin (g)		
	1	2	4
C_{max} (µg/ml)	3.11 ± 0.38	6.84 ± 2.00	9.91 ± 0.73
T_{max} (h)	1.9	1.8	1.05
k_{el} (h ⁻¹)	0.011 ± 0.002	0.010 ± 0.001	0.010 ± 0.002
$t_{1/2}$ (h)	64.8	72.2	69.3
AUC _{0-∞} (µg · h/ml)	23 ± 4	46 ± 9	82 ± 15
AUMC _{0-∞} (µg · h ² /ml)	1,239 ± 488	2,499 ± 691	5,050 ± 1691
V_{ss} (liters/kg)	30.1 ± 5.2	30.5 ± 7.6	38.3 ± 4.6
CL _t (ml/min/kg)	10.1 ± 0.9	9.5 ± 1.4	11.0 ± 1.9

^a Six subjects received 1 g of azithromycin, six received 2 g, and five received 4 g.
^b C_{max} , peak concentration of the drug.

unclear. Nonetheless, the macrolide-associated gastrointestinal symptomatology has been temporally related to a rise in motilin levels.

In the present study, there was a relatively low extent of gastrointestinal symptoms reported by the subjects. Serum motilin levels did not appreciably change with dose or concentration of azithromycin. Thus, these data do not support or refute an interaction between azithromycin and motilin.

Two-hour intravenous infusions of azithromycin produced dose-dependent concentrations of drug in serum. The mean T_{max} s closely approximated the end of the 2-h infusion for subjects administered 1 and 2 g of azithromycin. However, there was an apparent decrease in T_{max} s for subjects administered 4 g of azithromycin. Given the large volume administered over a relatively short period of time (4 liters in 2 h), the shortened T_{max} s were likely artifacts due to the dilutional effect of the infusate volume.

Azithromycin was detected in serum for the entire duration of sampling (240 h, or 10 days) in most subjects, reflecting the low terminal k_{el} . Consistent with previous reports (3, 11), the terminal $t_{1/2}$ was estimated to be 69 h. The similarity of values for k_{el} , V_{ss} , and CL_t and the low variability of the estimates of these parameters indicate that the pharmacokinetics of intravenous azithromycin are constant over the dose range of 1 to 4 g.

These data are in good agreement with those reported previously after single 500-mg intravenous doses in six healthy volunteers: $k_{el} = 0.0102$ h⁻¹, $t_{1/2} = 68$ h, $V_{ss} = 31.1$ liters/kg, and CL_t = 629 ml/min (7). Since the CL_t (approximately 750 ml/min) of azithromycin was not particularly low, the long elimination $t_{1/2}$ is attributed to the very large volume of distribution (2,300 liters). These data suggest that the long $t_{1/2}$ of azithromycin is due to the extensive uptake and slow release of the drug from tissues rather than to intrinsic inability to clear the drug.

The in vitro MICs at which 90% of isolates are inhibited (MIC₉₀s) for *Haemophilus influenzae* and *Streptococcus pneumoniae* are 0.5 and 0.12 µg/ml, respectively (2); concentrations of drug in serum in excess of 0.4 µg/ml can be achieved after 5 days of dosing (500 mg on day 1 followed by 250 mg/day for four more days) (4). Because azithromycin accumulates within tissues at high concentrations and has a long $t_{1/2}$, breakpoints for susceptibility of an organism to azithromycin based upon concentrations in serum may not be clinically valid. A susceptibility MIC₉₀ breakpoint of ≤0.12 µg/ml would typically be applied to azithromycin on the basis of levels in serum alone; however, a MIC₉₀ breakpoint of ≤2 µg/ml for susceptibility

has been proposed because of the expected tissue concentrations (1). Indeed, concentrations ranging from 4 to 8 $\mu\text{g/g}$, or approximately 100-fold those found in serum, have been found in tonsillar, pulmonary, prostatic, renal, and gynecological tissues 24 to 96 h after a single oral 500-mg dose (5).

Altogether, single doses of up to 4 g of azithromycin administered intravenously to healthy male volunteers were well tolerated. Quantifiable concentrations persisted for 10 days in most subjects, reflecting the extensive tissue uptake and slow release of azithromycin from tissue compartments.

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