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Multiple-Dose Pharmacokinetics of Ciprofloxacin Administered Intravenously to Normal Volunteers

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We administered multiple doses of ciprofloxacin intravenously over 30 min every 12 h for 1 week to nine healthy volunteers. Three volunteers received a placebo (vehicle) intravenously. Doses of 100, 150, and 200 mg were evaluated with a 1-week wash-out period intervening between each dose level. Terminal excretion half-lives averaged 3.67 ± 0.65, 3.60 ± 0.26, and 4.00 ± 0.69 h for the 100-, 150-, and 200-mg doses, respectively. Serum clearances were 30.1 ± 3.4, 29.8 ± 4.0, and 26.9 ± 4.1 liters/h per 1.73 m^2 for these doses. Urine concentrations remained in excess of the MIC for 90% of the relevant urinary tract pathogens for the full 12-h dosing interval at each dose. Renal clearance accounted for 56 to 71% of the serum clearance. However, because a microbiologic assay was used and biologically active, renally excreted metabolites were identified, the renal clearance determinations are likely to be in excess of the true values. The doses of ciprofloxacin administered intravenously were well tolerated, and the drug concentrations appeared adequate for the treatment of the vast majority of cases of nosocomially acquired sepsis and urinary tract infections. For patients with serious *Pseudomonas* infections and perhaps staphylococcal infections, either an 8-h dosing schedule or larger doses on a 12-h schedule should be considered.

Ciprofloxacin is a new quinoline carboxylic acid derivative, active against the *Enterobacteriaceae*, *Pseudomonas aeruginosa* (1, 3), and both methicillin-susceptible and -resistant *Staphylococcus aureus* (5). In vitro testing has shown that this drug is rapidly bactericidal against both resting and actively growing cultures (H.-J. Zeiler and K. Grohe, Abstr. Annu. Meet. Am. Soc. Microbiol., 1983, A17, p. 3). Because its spectrum includes the most common nosocomially acquired pathogens, this agent appears promising for the empiric therapy of nosocomially acquired sepsis. We evaluated the multiple-dose pharmacokinetics of this drug in normal volunteers at three different doses, which are likely to be useful for the critically ill septic patient.

MATERIALS AND METHODS

Volunteers. Healthy men (12) between 18 and 46 years old volunteered for this study; 9 of the 12 were randomly assigned to receive ciprofloxacin, whereas the other 3 subjects received a placebo (vehicle) in all study periods. The nine who received ciprofloxacin weighed between 54.8 and 73.0 kg and were not obese. The study was approved by an institutional review committee, and written informed consent was obtained according to institutional guidelines.

Study design. Subjects participated sequentially in week-long, double-blind studies involving three dose levels of ciprofloxacin (100, 150, 200 mg). Initially, 100 mg of ciprofloxacin was administered intravenously (i.v.) over 30 min every 12 h. This continued for 7 days. This was followed by a 7-day wash-out interval. Subsequently, volunteers similarly received 150- and 200-mg doses every 12 h for 1 week.

Safety evaluation. Physical examinations were made before drug administration and after the last dose on day 7, and vital signs were monitored at 0, 2, 4, 8, and 12 h after the morning dose on days 1, 4, and 7. Electrocardiograms were performed before the first dose was administered and 24 h after the last dose. Complete ophthalmological examinations, including visual acuity, color perception, and ophthalmoscopy, were performed before dosing on day 1 and 24 h after the last dose. The hematological tests and chemistry profiles of serum performed during the screening procedure were repeated before the morning dose on days 1 and 4 and 24 h after the last dose during each phase of dosing. Creatinine clearances were determined before the first and after the last dosing phases. Complete urinalysis was performed daily on specimens collected 0 to 2 h after dosing. In addition, the subjects were questioned daily regarding any adverse effects and were given diaries in which to record any unusual symptoms or adverse experiences for each day of dosing.

Sample acquisition. On days 1, 4, and 7 of each of the three dosage regimens, blood samples were obtained for serum immediately before and then at 5, 10, 15, 30, and 45 min and at 1, 2, 4, 8, and 11.5 h after the end of the infusion of the morning dose of ciprofloxacin. On the same days, urine was collected immediately before and then quantitatively during 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h postdose.

Antibiotic assay. After collection, the serum was promptly separated and frozen at −20°C until assayed. Urine collections were measured, and samples were frozen at −20°C until assayed. Concentrations of antibiotic in serum and urine were determined by a modified agar well diffusion assay described by Bennett et al. (2). *Klebsiella pneumoniae* ATCC 10031 was used as the indicator organism, and the agar was antibiotic medium C (neomycin assay agar, BBL Microbiology Systems, Cockeysville, Md.). Large (8- by 8-in. [20.32- by 20.32-cm]) bioassay plates were used for the determinations so that at least four replicates of each standard and unknown could be performed on the same plate. All

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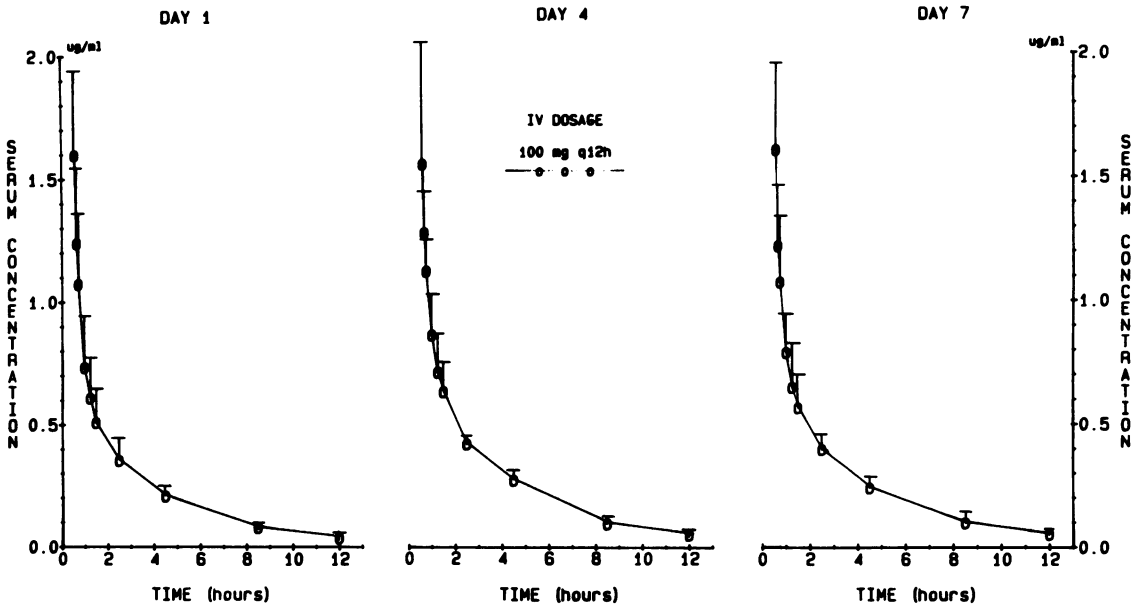

FIG. 1. Mean serum concentration-time profile of ciprofloxacin as determined in three dosing intervals in nine healthy volunteers receiving 100 mg in 30-min infusions every 12 h for 13 doses.

standards and unknowns for serum determinations were diluted in pooled human sera, and urine standards were diluted in phosphate buffer. The interassay percent coefficient of variation was 12.6 at 0.02 μg/ml and 6.3 at 1.4 μg/ml.

Pharmacokinetic analysis. At each dose level (100, 150, and 200 mg per dose), each patient had pharmacokinetic parameters determined by simultaneously fitting all serum concentrations obtained on day 1 plus day 4 plus day 7. A linear, two-compartment open model with elimination from the central compartment was used. The modeling procedure was accomplished by means of an iterative, nonlinear, weighted, least-squares regression technique, a variant of the ADAPT package of D'Argenio and Schumitzky (4). Hybrid pharmacokinetic parameters were calculated by standard methods (6). Renal clearances were calculated as amount of drug excreted into the urine over the dosing interval divided by the area under the fitted serum concentration-time curve for that same dosing interval.

Statistical analysis. Pharmacokinetic parameters were examined for differences between dose levels by repeated-measures analysis of variance. When different dose levels were being compared, an alpha of least 0.05 was deemed appropriate. When multiple pairwise comparisons were made, the Bonferroni adjustment for multiple pairwise comparisons within a data set was used (9).

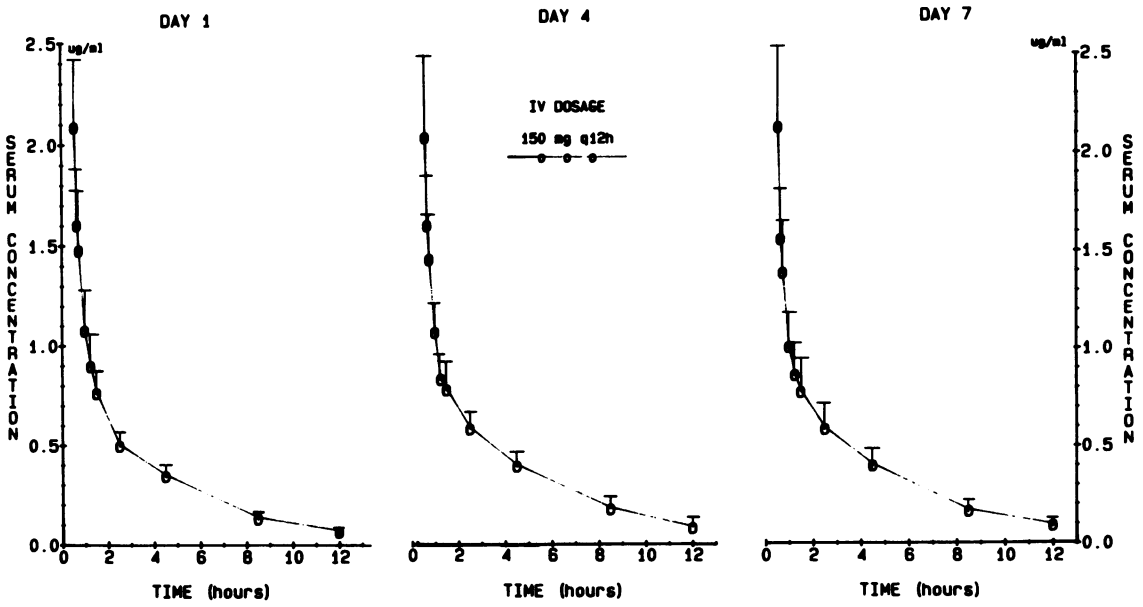

FIG. 2. Mean serum concentration-time profile of ciprofloxacin as determined in three dosing intervals in nine healthy volunteers receiving 150 mg in 30-min infusions every 12 h for 13 doses.

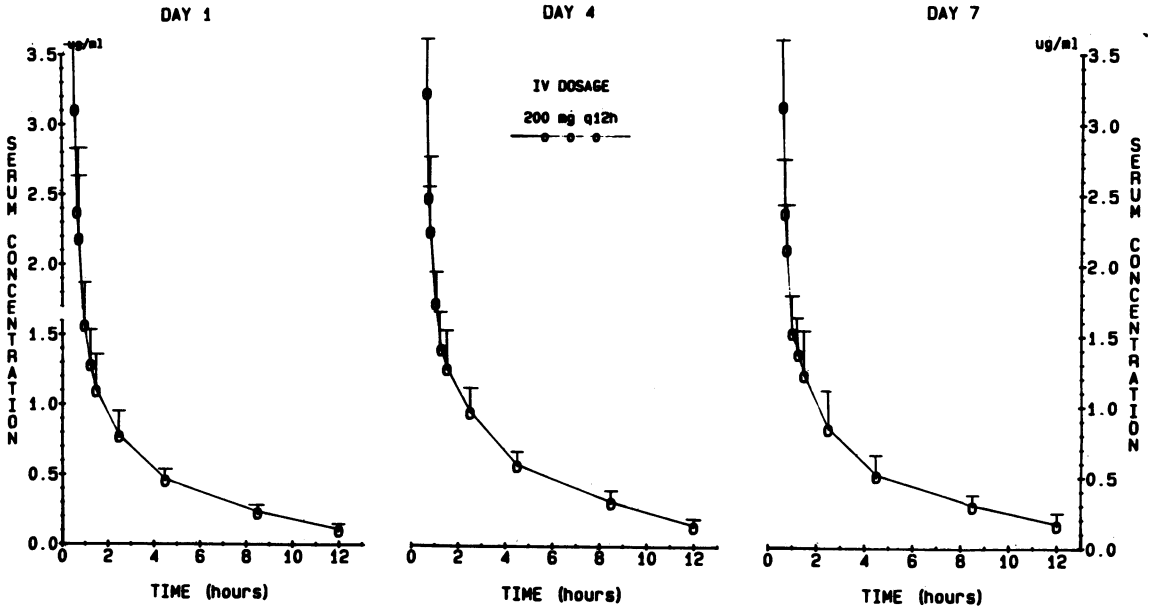

FIG. 3. Mean serum concentration-time profile of ciprofloxacin as determined in three dosing intervals in nine healthy volunteers receiving 200 mg in 30-min infusions every 12 h for 13 doses.

RESULTS

Concentrations in serum and urine. The mean drug concentration in serum for each time point sampled and for each dosing interval at each dose are shown in Fig. 1 through 3. The mean fractional urinary concentrations of ciprofloxacin for each dose and the dosing interval are shown in Table 1. It should be noted that four metabolites of ciprofloxacin have been identified in the urine, and three have been shown to possess microbiologic activity approximately 1/4 to 1/10 that of the parent compound. Hence, renal concentrations determined by bioassay are inappropriately large (Proc. Ciprofloxacin Workshop, Tokyo, Japan, 1984).

Recent observations by Joos et al. (8) indicate that a microbiologic assay overestimates urinary concentrations by 50% (i.e., true values are approximately two-thirds of those reported here). Also, in normal volunteers, no interference by metabolites could be detected in the serum.

Pharmacokinetic parameters. The pharmacokinetic parameters derived from all available concentrations in serum for each of the three doses are shown in Table 2. For the 100-mg dose, the volume of the central compartment averaged (± standard deviation) 39.0 ± 14.9 liters, a fractional volume of 0.63 ± 0.27 liter/kg. The serum clearance was 30.1 ± 3.4 liters/h per 1.73 m^2 and the terminal elimination half-life averaged 3.67 ± 0.65 h. For the 150-mg dose, the volume of the central compartment averaged 31.1 ± 12.4 liters, and this represented a fractional volume of 0.49 ± 0.17 liter/kg. The serum clearance for the 150-mg dose averaged 29.8 ± 4.0 liters/h per 1.73 m^2 and the terminal elimination half-life was 3.6 ± 0.26 h. For the 200-mg dose, the volume of the central compartment averaged 33.5 ± 2.4 liters (0.53 ± 0.17 liters/kg). The serum clearance for this dose averaged 26.9 ± 4.1 liters/h per 1.73 m^2 and the terminal excretion half-live was 4.0 ± 0.69 h.

The renal clearance and the percentage of serum clearance accounted for by renal clearance are shown in Table 3. In general, the renal clearance accounted for between 56 and 71% of the observed serum clearance. For the 100-mg dose on day 1, the renal clearance averaged 19.5 ± 5.7 liters/h per 1.73 m^2 and the renal clearance-to-serum clearance ratio was 58.0 ± 11.2%. On day 4, these values were 19.0 ± 3.4 liters/h per 1.73 m^2 and 66.9 ± 7.9%, respectively. On day 7, these values were 18.0 ± 3.6 liters/h per 1.73 m^2 and 59.8 ±

TABLE 1. Mean urinary concentrations[a] of ciprofloxacin in nine volunteers

Dose (mg)	Day of dose	Ciprofloxacin concn at time (h) after dosing:						
		0–2	2–4	4–8	8–12	12–16	16–24	24–48
100	1	158.67 ± 136.78	72.89 ± 31.24	32.47 ± 12.50	9.26 ± 4.52			
	4	167.83 ± 154.68	64.61 ± 43.94	22.36 ± 15.12	7.14 ± 4.08			
	7	81.31 ± 62.86	74.83 ± 42.34	28.90 ± 21.29	6.99 ± 3.24	7.41 ± 4.15	4.44 ± 2.75	0.76 ± 0.26
150	1	139.56 ± 134.04	59.25 ± 30.49	31.77 ± 16.56	5.97 ± 3.68			
	4	112.47 ± 106.96	67.50 ± 51.43	40.56 ± 20.66	12.33 ± 6.93			
	7	173.67 ± 154.88	91.22 ± 53.18	36.64 ± 18.79	10.08 ± 5.28	8.90 ± 4.33	4.77 ± 3.81	1.23 ± 0.42
200	1	198.50 ± 148.46	84.00 ± 65.94	43.19 ± 12.72	12.56 ± 4.93			
	4	363.94 ± 279.80	112.58 ± 73.14	48.66 ± 27.92	18.80 ± 9.20			
	7	158.72 ± 85.05	93.89 ± 31.05	70.72 ± 60.27	22.72 ± 13.57	17.89 ± 9.13	7.38 ± 3.72	1.55 ± 0.77

[a] Expressed as micrograms per milliliter of total antimicrobial activity (includes ciprofloxacin metabolites).

TABLE 2. Pharmacokinetic parameters for ciprofloxacin as determined in nine volunteers receiving 100; 150; and 200-mg doses i.v. every 12 h for 7 days[a]

Dose (mg)	V_c (liters/kg)	V_{area} (liters/kg)	V_{ss} (liters/kg)	AUC_∞ (μg · h/ml)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Serum clearance (liters/hr per 1.73 m^2)
100	0.63 ± 0.27	2.56 ± 0.68	1.95 ± 0.48	3.40 ± 0.49	0.29 ± 0.14	3.67 ± 0.65	30.1 ± 3.4
150	0.49 ± 0.17	2.45 ± 0.33	1.97 ± 0.25	5.14 ± 0.77	0.18 ± 0.06	3.60 ± 0.26	29.8 ± 4.0
200	0.53 ± 0.17	2.47 ± 0.58	1.97 ± 0.42	7.70 ± 1.38	0.22 ± 0.08	4.00 ± 0.69	26.9 ± 4.1

[a] Serum parameter values (mean ± standard deviation) were obtained from the best fit of all sampled points. V_c, Volume of distribution of the central compartment; V_{area}, volume of distribution of drug in the body; V_{ss}, volume of distribution at steady state; AUC_∞, area under the serum concentration-time curve; $t_{1/2\alpha}$ and $t_{1/2\beta}$, distribution and elimination half-lives, respectively.

7.7%. For the 150-mg dose, on days 1, 4, and 7, the renal clearances were 18.4 ± 4.0, 20.3 ± 5.0, and 17.7 ± 2.4 liters/h per 1.73 m^2. The percentages of serum clearance accounted for by renal clearance were 56.0 ± 6.9, 68.1 ± 9.8, and 60.5 ± 8.8 on days 1, 4, and 7, respectively. For the 200-mg dose on day 1, the renal clearance was 18.8 ± 3.1 liters/h per 1.73 m^2. On days 4 and 7, this value was 17.4 ± 3.4 and 19.1 ± 4.9 liters/h per 1.73 m^2, respectively. The percentages of serum clearance accounted for as renal clearance were 63.2 ± 5.3 for day 1, 67.6 ± 10.4 for day 4, and 71.0 ± 8.1 for day 7.

Statistical analysis. The repeated measures analysis of variance comparing serum parameters by dose size did not identify any significant differences for any parameter tested. For renal clearance and serum clearance-to-renal clearance ratio, no significant differences were present across doses.

Toxicity evaluations. Ciprofloxacin was well tolerated throughout the study period. No clinically significant changes were observed during any of the physical or ophthalmological examinations or in the results of laboratory tests. Occasional erythema and induration at the infusion site were noted in the ciprofloxacin-receiving group, but in no case did these require withdrawal from the study.

DISCUSSION

Ciprofloxacin is a new quinoline carboxylic acid derivative with a broad spectrum of activity. MICs for common bacteremic pathogens in general range between 0.01 to 2 μg/ml (1, 3, 5). Ciprofloxacin is also available in both oral and i.v. dosage forms so that patients treated in the hospital may be discharged on the oral medication. Multiple-dosing studies with 250, 500, and 750 mg of ciprofloxacin orally twice a day have been performed at our institution and have demonstrated that in this form the drug is safe and well tolerated and produces a serum concentration-time profile which would be predicted to be adequate for treatment against the vast majority of bacteremic pathogens, particularly at the higher dosages (7).

TABLE 3. Renal clearance[a] of ciprofloxacin as determined in nine volunteers receiving 100, 150, and 200-mg doses i.v. every 12 h for 7 days

Day (mg)	Day of dose	Renal clearance ± SD (liters/h per 1.73 m^2)	Renal clearance/serum clearance ratio (%)
100	1	19.5 ± 5.7	58.0 ± 11.2
	4	19.0 ± 3.4	66.9 ± 7.9
	7	18.0 ± 3.6	59.8 ± 7.7
150	1	18.4 ± 4.0	56.0 ± 6.9
	4	20.3 ± 5.0	68.1 ± 9.8
	7	17.7 ± 2.4	60.5 ± 8.8
200	1	18.8 ± 3.1	63.2 ± 5.3
	4	17.4 ± 3.4	67.6 ± 10.4
	7	19.1 ± 4.9	71.0 ± 8.1

[a] Renal clearances are calculated by using total antimicrobial activity and include ciprofloxacin metabolites.

In this investigation, we examined the multiple-dose pharmacokinetics of ciprofloxacin administered i.v. in the range of dosages we felt likely to be clinically useful. The terminal excretion half-life of 3.6 to 4 h noted for the three doses studied would support a 12-h dosing schedule. The volume of the distribution of the central compartment was large and averaged ca. 30 liters, and no appreciable differences were noted between doses. The serum clearances were high (averaging 25 to 30 liters/h per 1.73 m^2), with 60 to 70% of the serum clearance being accounted for as renal clearance (it should be noted that our renal clearances are inappropriately high because of the bioassay used, which measures total activity of parent compound and metabolites). The renal clearance was far in excess of creatinine clearance, implying an active secretory process into the urine. There were no differences noted between dose sizes for either serum clearance or renal clearance.

When one compares the serum concentration-time profiles generated with the doses we employed, it is apparent that the drug concentration exceeded the MIC for 90% of the clinically important pathogens, such as *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and the *Proteeae*, for the entire 12-h dosing interval. However, for pathogens requiring higher MICs, such as *P. aeruginosa* and *S. aureus*, serum levels fell below the MIC for 90% of the pathogens after approximately 2 to 4 h, even for the 200-mg dose. Even though ciprofloxacin has recently been shown to possess a postantibiotic effect for both *S. aureus* and *P. aeruginosa* of approximately 1.5 to 4 h, a dose higher than 200 mg i.v. every 12 h may be desirable for some infections with these pathogens (S. Gudmundsson, B. Vogelman, and W. Craig, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1120, 1984).

Simulations with the mean pharmacokinetic parameters developed in our study population revealed that with a dosing schedule of 200 mg i.v. every 8 h, serum ciprofloxacin concentrations should remain above 0.5 μg/ml for approximately 6 h at steady state. When coupled with the postantibiotic effect which has been demonstrated for this compound against both *Staphylococcus* spp. and *P. aeruginosa*, the vast majority of serious infections caused by these pathogens should be amenable to therapy with ciprofloxacin at a dosing schedule of 200 mg every 8 h.

In conclusion, ciprofloxacin was safe and well tolerated when used in a multiple-dosing fashion at the dosing schedule we used over a period of 1 week. When evaluating different doses (100, 150, or 200 mg), we found that the drug behaved in a dose-linear fashion, had a terminal excretion half-life of 3.5 to 4 h, and produced a serum concentration-time profile adequate for the therapy of the vast majority of infections caused by the *Enterobacteriaceae*. In most serious infections, a dose of 200 mg given every 12 h should be adequate. For serious infections caused by some pseudomonads and *S. aureus*, 200 mg every 8 h might be a preferable schedule. When one considers the microbiologic activity and pharmacokinetic profile of ciprofloxacin, it is clear that this agent holds promise for the therapy of serious, nosocomially acquired infections and is deserving of extensive clinical investigation.

ACKNOWLEDGMENT

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