

## Pharmacokinetics of High-Dose Intravenous Ciprofloxacin in Young and Elderly and in Male and Female Subjects

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Received 26 August 1994/Returned for modification 27 November 1994/Accepted 8 January 1995

**The effects of age and gender on the pharmacokinetics of high-dose intravenous ciprofloxacin in a healthy volunteer study were investigated. Plasma ciprofloxacin concentrations were higher in the elderly than in the young, and the pharmacokinetic parameters were not significantly different between the genders. Ciprofloxacin was well tolerated, with the majority of adverse events related to local reactions at the IV site.**

Ciprofloxacin, the first oral broad-spectrum fluoroquinolone for the treatment of moderate to serious gram-positive and gram-negative infections, was first marketed in the United States in 1987 (4). The currently approved dosage for intravenous ciprofloxacin in the United States is 200 to 400 mg given every 12 h. Recently a higher dosage regimen of 400 mg every 8 h for the treatment of severe respiratory tract infections was investigated (5). This unapproved intravenous ciprofloxacin regimen was shown to be clinically superior to one with imipenem-cilastin, and it demonstrated excellent tolerability (5). The primary objective of this study was to determine the effect of age on the pharmacokinetics of higher-dose intravenous ciprofloxacin by comparing the pharmacokinetic dispositions in elderly (>65 years of age) and young (18 to 40 years of age) subjects. The effect of gender on the pharmacokinetics of higher-dose intravenous ciprofloxacin was also investigated by comparing the pharmacokinetic profiles of males and females among both the elderly and the young subjects. The tolerability of higher doses of intravenous ciprofloxacin following single dosing and multiple dosing of 400 mg every 8 h in young and elderly subjects was also assessed.

Twenty-four healthy subjects participated in the study. They were divided into two groups as follows: 12 young subjects, ages 18 to 40 (six males and six females), and 12 elderly subjects, aged >65 years (six males and six females). The subjects were judged to be healthy on the basis of the results of a complete physical examination, a medical history, a 12-lead electrocardiogram, laboratory tests (hematology, blood chemistry, and urinalysis), a urine drug screen, a hepatitis screen, and a human immunodeficiency virus screen. Pregnant females were excluded from the study. The protocol was approved by the Human Research Committee, Millard Fillmore Hospital, Buffalo, N.Y. Written informed consent was obtained from the subjects prior to enrollment in this study.

Subjects entered the clinic in the morning on day 0 prior to the first dose and remained confined until 24 h after the last dose. On day 0, a 24-h period of urine collection for the determination of creatinine clearance ( $CL_{CR}$ ) was started. On day 1, all subjects received a single 400-mg dose (in 200 ml) of intravenous ciprofloxacin infused for 1 h. Blood and urine samples were collected over the next 24 h to assess the single-dose pharmacokinetic profile. On day 2, subjects began the

multiple-dose regimen consisting of intravenous ciprofloxacin at 400 mg every 8 h. Dosing every 8 h was continued through days 3 and 4, with the final dose administered on the morning of day 5. All subjects received a total of 11 intravenous doses of ciprofloxacin. Use of medications other than acetaminophen and birth control pills was prohibited during the study. Subjects were allowed up to three cups of coffee or caffeine-containing soft drink during each 24-h period.

Following the single dose on day 1 and the final dose on day 5, serial venous blood samples and urine samples were collected. The samples were stored at  $-20^{\circ}\text{C}$  until analyzed. Urine samples for the examination of ciprofloxacin crystals were also collected. Subjects were questioned in a systematic but nonspecific way each day about possible adverse or unusual effects. The IV site was examined routinely, and any local reactions were recorded.

Plasma ciprofloxacin concentrations were determined by a sensitive and specific high-performance liquid chromatography method with fluorescence detection. After precipitation of the plasma proteins with a mixture of acetonitrile and perchloric acid, the extract was injected onto a Waters C18  $\mu$ Bondapak column (10- $\mu\text{m}$  particle size; 3.9 by 150 mm) preceded by an Alltech C18 guard column. The mobile phase consisted of acetonitrile, methanol, and 0.1 M citric acid (1:5.25:18.75) containing 0.54 g of ammonium perchlorate per liter and 0.65 ml of tetrabutylammonium hydroxide per liter. The flow rate was 1.0 ml/min. A fluorescence detector with an excitation wavelength of 270 nm and an emission wavelength of 440 nm was used to monitor column eluant. Abbott compound 56619 was used as an internal standard. The assay was linear over the range of 0.05 to 10  $\mu\text{g/ml}$ . The mean variability of the standards for this study was 2.05% with a maximum variability of 4.19% at 0.1  $\mu\text{g/ml}$ . The mean variability of the quality control samples for this study was 5.49% with a maximum variability of 6.67% at 0.15  $\mu\text{g/ml}$ .

The pharmacokinetic parameters were calculated by non-compartmental methods. The steady-state volumes of distribution ( $V_{ss}$ ) on days 1 and 5 were calculated on the basis of equations described by Smith and Schentag (10).

For each pharmacokinetic parameter, logarithmically transformed estimates for each subject were analyzed by using a one-way analysis of variance based on an age-by-gender grouping. Means were compared between the young and elderly groups and between genders for each age group. Each comparison of means included a 90% confidence interval surrounding the ratio of means and a two-tailed test of equality of the means. Age-by-gender interaction was also tested.

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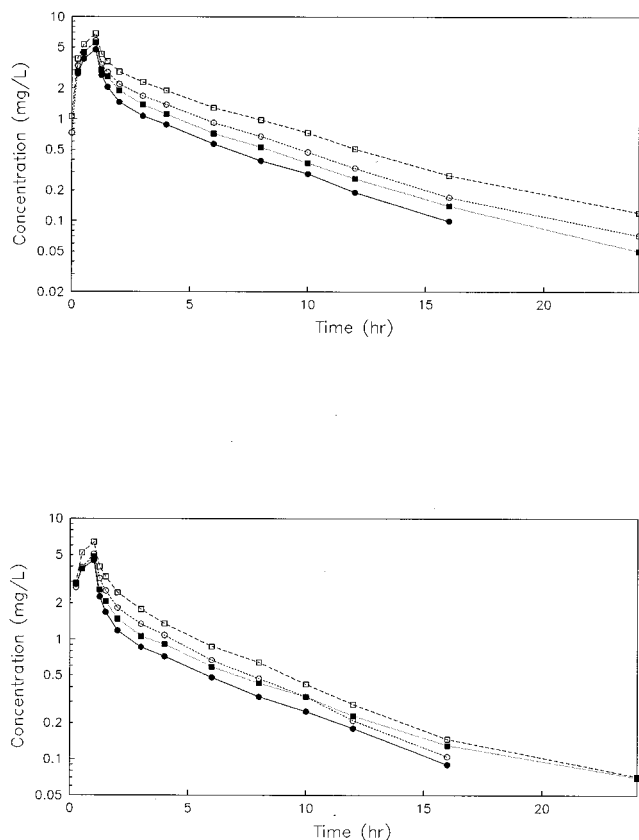


FIG. 1. (Top panel) Mean ciprofloxacin concentrations in young subjects on day 1 (●) and day 5 (○) and in elderly subjects on day 1 (■) and day 5 (□). Subjects were administered 400 mg of intravenous ciprofloxacin every 8 h for 5 days. (Bottom panel) Mean ciprofloxacin concentrations in young male subjects (●), young female subjects (○), elderly male subjects (■), and elderly female subjects (□) on day 1 following a 400-mg intravenous dose of ciprofloxacin. At 24 h, all volunteers in some of the groups did not have detectable concentrations, and hence mean values are not reported for these groups.

The mean ages were as follows: young males, 24.7 years; young females, 26.8 years; elderly males, 67.7 years; and elderly females, 68.8 years. The mean  $CL_{CR}$  values were as follows: young males, 132.3 ml/min/1.73 m<sup>2</sup>; young females, 95.8 ml/min/1.73 m<sup>2</sup>; elderly males, 93.6 ml/min/1.73 m<sup>2</sup>; and elderly females, 69 ml/min/1.73 m<sup>2</sup>. All 24 subjects completed the study, and data from all subjects are included in the pharmacokinetic analysis.

Mean plasma ciprofloxacin concentration versus time plots for the young and elderly groups and the mean day 1 concentrations for male and female and young and elderly subjects are presented in Fig. 1. The pharmacokinetic parameters for the young and elderly groups are presented in Table 1. The data indicate that values for maximum concentration in plasma ( $C_{max}$ ),  $C_{max}$  normalized to dose (milligrams per kilogram of body weight) ( $C_{max, norm}$ ), area under the plasma concentration curve from 0 to 8 h ( $AUC_{0-8}$ ), and  $AUC_{0-8}$  normalized to dose (milligrams per kilogram) ( $AUC_{norm}$ ) were significantly higher for elderly subjects than for young subjects on both days 1 and 5. The mean total body clearance (CL), renal clearance ( $CL_R$ ), and  $V_{ss}$  values were significantly lower for the elderly than for the young.

Day 1 pharmacokinetic parameters for males and females are presented in Table 2. Within each age group, the  $C_{max, norm}$  values for males and females were similar. In both the young and elderly groups, the  $AUC_{0-8}$  and AUC for 0 h to infinity ( $AUC_{0-\infty}$ ) values for female subjects were significantly higher (28 to 46%) than those for the male subjects. However, the  $AUC_{norm}$  values for the male and female subjects were not significantly different. Values for CL normalized to body weight were similar for males and females within each age group, indicating that there were no pharmacokinetic differences due to gender when body weight is taken into consideration. The  $CL_R$  for the young females was significantly higher than that for elderly females, probably because of differences in  $CL_{CR}$  between the two groups; the mean  $CL_{CR}$  for young females was 95.8 ml/min/1.73 m<sup>2</sup>, and that for elderly females was 68.9 ml/min/1.73 m<sup>2</sup>. In general there was little indication of gender-by-age group interaction. The differences between age groups were similar for both males and females.

Exploratory regression analyses between the pharmacokinetic parameters and age, weight, and  $CL_{CR}$  were performed. Of particular interest was the plot showing CL on day 1 as a function of baseline  $CL_{CR}$ , as shown in Fig. 2. A positive correlation between CL and  $CL_{CR}$  was observed where  $CL = 0.173 \cdot CL_{CR} + 11.67$  ( $P < 0.001$ ).

No ciprofloxacin crystals were found in the urine samples, which were collected 2 h following the morning dose on days 2, 3, and 4. All 24 subjects were included in the analysis of safety. Each subject received 11 doses of 400 mg over a period of 5 days. None of the adverse events were judged to be severe in intensity, and no subjects were withdrawn from the study because of an adverse event. There were no serious or unexpected adverse events. Most of the adverse events were related to IV injection site reactions (e.g., erythema at the IV site, IV infiltration, IV induration, and thrombophlebitis). All of these

TABLE 1. Mean pharmacokinetic parameters for the young (female and male combined) and elderly (female and male combined) groups<sup>a</sup>

Group and time of sampling	$C_{max}$ (mg/liter)	$C_{max, norm}$ (mg/liter)/(mg/kg)	$AUC_{0-8}$ (mg · h/liter)	$AUC_{norm}$ (mg · h/liter)/(mg/kg)	$t_{1/2}$ (h) <sup>b</sup>	$V_{ss}$ (liters)	CL (liters/h)	$CL_R$ (liters/h)	$CL_{NR}$ (liters/h) <sup>c</sup>
Young									
Day 1	4.84 (16) <sup>d</sup>	0.83 (18) <sup>d</sup>	10.4 (17) <sup>d</sup>	2.16 (13) <sup>d</sup>	3.98 (14) <sup>d</sup>	142 (18) <sup>d</sup>	31.5 (17) <sup>d</sup>	14.1 (21) <sup>d</sup>	15.9 (51)
Day 5	5.85 (18) <sup>e</sup>	1.00 (12) <sup>e</sup>	14.6 (18) <sup>e</sup>	2.48 (12) <sup>e</sup>	4.70 (13) <sup>e</sup>	125 (25) <sup>e</sup>	27.4 (18) <sup>e</sup>	13.4 (17) <sup>e</sup>	13.8 (28)
Elderly									
Day 1	5.63 (21) <sup>d</sup>	1.09 (20) <sup>d</sup>	12.7 (23) <sup>d</sup>	3.13 (16) <sup>d</sup>	4.78 (17) <sup>d</sup>	129 (28) <sup>d</sup>	24.8 (21) <sup>d</sup>	9.78 (40) <sup>d</sup>	14.5 (24)
Day 5	6.83 (17) <sup>e</sup>	1.32 (15) <sup>e</sup>	19.0 (21) <sup>e</sup>	3.69 (18) <sup>e</sup>	5.10 (12) <sup>e</sup>	110 (23) <sup>e</sup>	21.0 (21) <sup>e</sup>	9.11 (30) <sup>e</sup>	11.5 (32)

<sup>a</sup> Values in parentheses are percents coefficient of variation.

<sup>b</sup>  $t_{1/2}$ , half-life.

<sup>c</sup>  $CL_{NR}$ , nonrenal clearance.

<sup>d</sup>  $P < 0.05$  for comparison between young and elderly on day 1.

<sup>e</sup>  $P < 0.05$  for comparison between young and elderly on day 5.

TABLE 2. Mean pharmacokinetic parameters for young males, young females, elderly males, and elderly females following a single 400-mg intravenous dose of ciprofloxacin<sup>a</sup>

Group	C <sub>max</sub> (mg/liter)	C <sub>max, norm</sub> (mg/liter)/ (mg/kg)	AUC <sub>0-∞</sub> (mg · h/liter)	AUC <sub>norm</sub> (mg · h/liter)/ (mg/kg)	t <sub>1/2</sub> (h) <sup>b</sup>	V <sub>ss</sub> (liters/kg)	CL (liters/h/kg)	CL <sub>R</sub> (liters/h/kg)	CL <sub>NR</sub> (liters/h/kg) <sup>c</sup>
Young									
Male	4.65 (14)	0.90 (14)	11.2 (6) <sup>d,e</sup>	2.16 (11) <sup>e</sup>	4.32 (13) <sup>d,e</sup>	2.13 (6)	0.46 (11) <sup>e</sup>	0.167 (23) <sup>d</sup>	0.290 (16) <sup>d,e</sup>
Female	5.06 (17) <sup>f</sup>	0.76 (18) <sup>f</sup>	14.4 (16) <sup>d,f</sup>	2.16 (16) <sup>f</sup>	3.67 (10) <sup>d,f</sup>	2.04 (11) <sup>f</sup>	0.46 (16) <sup>f</sup>	0.257 (17) <sup>d,f</sup>	0.187 (55) <sup>d</sup>
Elderly									
Male	4.85 (15) <sup>g</sup>	1.09 (22)	13.7 (6) <sup>e,g</sup>	3.07 (14) <sup>e</sup>	5.34 (11) <sup>e,g</sup>	1.83 (17) <sup>g</sup>	0.33 (14) <sup>e</sup>	0.128 (25)	0.192 (23) <sup>e</sup>
Female	6.54 (14) <sup>f,g</sup>	1.10 (19) <sup>f</sup>	19.0 (17) <sup>f,g</sup>	3.19 (19) <sup>f</sup>	4.27 (13) <sup>f,g</sup>	1.51 (20) <sup>f,g</sup>	0.31 (19) <sup>f</sup>	0.124 (48) <sup>f</sup>	0.180 (17)

<sup>a</sup> Values in parentheses are percents coefficient of variation.

<sup>b</sup> t<sub>1/2</sub>, half-life.

<sup>c</sup> CL<sub>NR</sub>, nonrenal clearance.

<sup>d</sup> P < 0.05 for males and females in the young group.

<sup>e</sup> P < 0.05 for males in the young and elderly groups.

<sup>f</sup> P < 0.05 for females in the young and elderly groups.

<sup>g</sup> P < 0.05 for males and females in the elderly group.

events were of mild intensity and self-limiting, and they resolved without any systemic treatment. The numbers of subjects with at least one local reaction were as follows: two young males, three young females, four elderly males, and five elderly females. In many of the subjects with injection site reactions there was more than one event during the 5-day study. Described in this section are some of the other types of adverse events. One young male had a fainting episode prior to dosing on day 4. A predose blood sample had been taken from this subject, and the subject went to void urine prior to dosing. The blood draw and the subject's lack of sleep might have resulted in this fainting episode. The attending physician on the scene attributed it to a vasovagal reaction. Another subject complained of moderate lightheadedness on days 2 and 3; on day 3 it resolved. This subject also developed a mild rash which appeared on day 2 and lasted until day 11 postdose, and this was judged to be not drug related. Other adverse events were mild and resolved spontaneously. Three events (headache, rash, and nasal congestion) were treated symptomatically. Three subjects had treatment-emergent liver enzyme elevations. These were mild (<1.8 times the upper limit of normal) and asymptomatic, and they resolved shortly after drug administration was terminated.

Age affects the distribution and elimination of many drugs because of physiological changes associated with aging. Organ function in the elderly generally declines as a result of advancing age, e.g., cardiac output decreases by 30 to 40% between

the ages of 25 and 65 years and the glomerular filtration rate declines progressively after 20 years of age. Body composition also changes with aging. Total body water and lean body mass levels are lower in the elderly (10 to 15% lower at age 80 than at age 20), both in absolute terms and as percentages of body weight. The decrease in lean body mass is associated with a corresponding increase in body fat. The reduction in the proportion of lean body mass per unit of total body weight has been shown to alter the volumes of distribution of several drugs (2).

Our study, with a higher intravenous ciprofloxacin dosage, has confirmed the findings reported by others who used the oral formulation or lower intravenous dosage regimens. As seen in previous studies (1, 8), the plasma ciprofloxacin concentrations in our study were higher in elderly subjects. Increases in the C<sub>max</sub> and AUC and an increase in the half-life were observed for the elderly subjects compared with the young. These changes were primarily due to a decrease in the CL in the elderly, in particular to a decrease in CL<sub>R</sub>. As shown in Fig. 2, there were correlations between CL and CL<sub>CR</sub> and also between CL<sub>R</sub> and CL<sub>CR</sub>. This was not unexpected, since renal function in the elderly population is reduced, and in healthy subjects the CL<sub>R</sub> of ciprofloxacin accounts for approximately 60% of total serum clearance (3). The V<sub>ss</sub> was also reduced in the elderly subjects compared with the young, probably because of reduction in the lean body mass per unit of total body weight in the elderly.

Ball et al. (1) reported twofold increases in C<sub>max</sub> and AUC for elderly subjects compared with young subjects following a 100-mg oral dose. LeBel et al. (8) reported increases in the AUC (approximately twofold), C<sub>max</sub> (43%), and elimination half-life (about twofold) for elderly subjects compared with young subjects following a 500-mg oral dose. The increases seen in these studies following oral administration were of a greater magnitude than those seen in the present study using intravenous ciprofloxacin. Following an oral dose, reduced first-pass metabolism in the elderly may add to the effect of lower CL<sub>CR</sub>. These two factors may be responsible for the approximately twofold increases in the C<sub>max</sub> and AUC seen in the studies of Ball et al. and LeBel et al. An increase in bioavailability of approximately 25%, i.e., a decrease in first-pass metabolism, was observed in the elderly in another study, that of Ljungberg and Nilsson-Ehle (9), in which single oral and intravenous 250-mg doses of ciprofloxacin were given to young and elderly subjects. Kitzes-Cohen et al. (7) reported a twofold increase in the AUC and a 75% increase in the C<sub>max</sub>

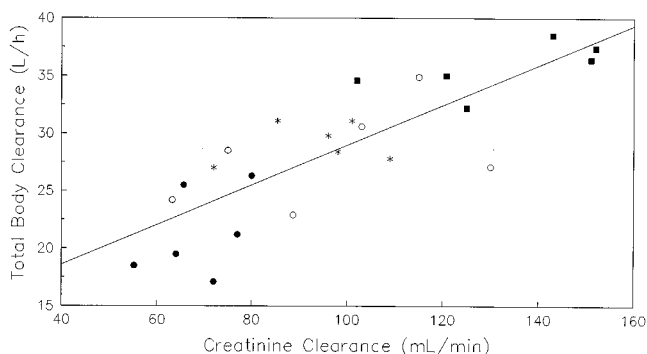


FIG. 2. Ciprofloxacin CL versus CL<sub>CR</sub>. The regression line is CL = CL<sub>CR</sub> · 0.173 + 11.67; r<sup>2</sup> = 0.6735. ■, young male; ○, young female; \*, elderly male; ●, elderly female.

following a single 200-mg intravenous dose for elderly subjects compared with young subjects. These increases are much higher than those seen in the present study and when intravenous doses of ciprofloxacin were administered in the study of Ljungberg et al., and they are not consistent with the present results or results of other investigators.

Two studies characterized the gender difference in the pharmacokinetics of ciprofloxacin following oral doses of 100, 250, 500, and 1,000 mg (6) or an intravenous dose of 200 mg (11). The results of the oral study (6) indicate that the concentrations in serum were slightly higher in females than in males, but when the  $C_{\max}$  and AUC were normalized to body weight there were no differences in these parameters between males and females. Another study was conducted following administration of a single 200-mg intravenous dose of ciprofloxacin to male and female subjects (11). The results of this study showed a significant decrease in  $CL_R$  and volume of distribution in the female subjects compared with the male subjects. However, these differences were mainly due to the lower body weights of the females. The pharmacokinetic parameters for the female and male groups in our study indicate that the concentrations in plasma were higher in the females than in the males. The  $C_{\max}$  and AUC values were higher for the females than for the males; however, when these parameters were normalized to the dose (milligrams per kilogram), they were not significantly different. Thus, these differences were apparently due to the difference in body weight between the two groups. These results are consistent with those observed in previous studies (6, 11). If a fixed dose (not based on body weight) is given to all subjects, the exposure of ciprofloxacin will be higher in females. Females also have reduced  $CL_{CR}$  and consequently decreased CL and  $CL_R$  of ciprofloxacin. This is particularly important for elderly females.

The results of this study demonstrate that the concentrations ( $C_{\max}$  and AUC) of ciprofloxacin in plasma following administration of 400 mg every 8 h are significantly higher (about 20 to 30%) in elderly subjects than in young subjects, primarily because of a decrease in the  $CL_R$ . Within the young and the elderly groups, the dose- and body weight-normalized parameters ( $C_{\max, \text{norm}}$ ,  $AUC_{\text{norm}}$ , CL, and  $V_{ss}$ ) were similar for males

and females, indicating that the differences between males and females were largely due to differences in body weight. Although an increase in concentrations in plasma was observed for the elderly group compared with the young and for females compared with males, the magnitude of this increase was only 20 to 30% and it is probably not clinically significant.

We thank Connie Hogan for monitoring the study and Ray Falk and Lee Kaiser for providing the statistical analysis.

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