Pharmacokinetics of Ofloxacin after Single and Multiple Intravenous Infusions in Healthy Subjects

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The pharmacokinetics of ofloxacin were investigated in eight healthy male volunteers. A single infusion (200 mg over 0.5 h) was performed on day 1, followed by a washout period of 2 weeks. Repeated administrations were performed for 4 days (200 mg every 12 h). Pharmacokinetic parameters were determined from the plasma decay curves of the single and the last of the multiple administrations. Ofloxacin kinetics after the single dose were best described by a two-phase curve with a total body clearance of 241.6 ± 43.3 ml min^{-1}, a volume of distribution of 112 ± 23.1 liters, and an elimination half-life of 5.4 ± 0.8 h. The extrapolated area under the curve ($AUC_{0-\infty}$) was 14 ± 2.3 mg · h liter^{-1}. The pharmacokinetics were not significantly modified by repeated administration, demonstrated mainly by the AUC_{0-12} value of the last infusion (13.4 ± 2.2 mg · h liter^{-1}). We conclude that, with intravenous multiple doses every 12 h, the steady state is reached within 24 to 36 h and no abnormal accumulation or changes in pharmacokinetic parameters occur.

Ofloxacin is a new fluoroquinolone carboxylic acid derivative with a broad spectrum of activity against gram-negative and gram-positive microorganisms (8). The pharmacokinetics of the oral form of this compound have been extensively studied in various situations in humans (3, 9; S. C. Flor, H. Weintraub, T. Marriott, N. Friedman, and B. Beals, Proc. 14th Int. Congr. Chemother., p. 25–26, 1985; A. Saito and M. Tomizawa, Proc. 13th Int. Congr. Chemother., p. 24–28, 1983), with special attention to extravascular diffusion (6) and tissue diffusion (1; L. Couraud, J. B. Fourtillan, M. C. Saux, A. Bryskier, and M. Vincent du Laurier, Proc. 14th Int. Congr. Chemother., p. 31–32, 1985). A parenteral formulation has recently been developed. The purpose of this study was to investigate the pharmacokinetic properties of the intravenous (i.v.) formulation of ofloxacin after both a single infusion and a multiple-dose administration schedule in healthy subjects.

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After written informed consent and national and local ethical committee approval had been obtained, eight healthy male subjects with no known allergy to quinolone derivatives were impaneled. They had normal hepatic and renal functions. They ranged in age from 21 to 27 years (mean ± standard deviation, 23.9 ± 2.3 years) and in body weight from 65 to 89 kg (mean ± standard deviation, 72.9 ± 8.0 kg). None of the subjects had taken any medication for at least 1 week prior to the study. Alcohol and tobacco were prohibited during the study.

The study was divided into two steps. The first step consisted of a single administration of ofloxacin (1 vial of 200 mg diluted in saline) by a 30-min i.v. infusion. Blood samples were drawn into glass tubes at 0, 0.5 (end of the infusion), 0.58, 1, 2, 4, 6, 12, 24, and 50 h after infusion. Urine was collected at time zero and then during four periods: 0 to 6, 6 to 12, 12 to 24, and 24 to 50 h after dosing. The subjects, who had fasted overnight, had breakfast 2 hours after administration; thereafter, food and drink were taken ad libitum. After a 2-week washout period, the second step consisted of

repeated administrations of ofloxacin (200 mg diluted in saline) by 30-min i.v. infusions every 12 h for 4 days (nine administrations). To monitor steady-state levels, blood samples were obtained just before each infusion (C_{min}) and at the end of the infusion time (C_{max}). After the last infusion, additional blood and urine samples were obtained according to the schedule described for the first step. Before and at the end of the study, the subjects underwent a complete physical examination and laboratory testing. Urine analysis included testing for creatinine clearance (CL_{CR}), excretion of N-acetyl-glucosaminidase, glutamyltransferase, and β_2-microglobulin. The presence of abnormal crystalluria was assessed at the end of the multiple-dose regimen with reference to pretherapy samples. The subjects were also questioned daily about any drug-induced side effects.

Samples were stored at $-20°C$ and assayed within 2 weeks.

Ofloxacin concentrations in serum and urine were measured by ion-paired reversed-phase liquid chromatography with fluorimetric detection by the method of Humbert et al. (G. Humbert, F. Borsa, W. Couet, and J. B. Fourtillan, Proc. 14th Int. Congr. Chemother., p. S41/3, 179, 1985). The lowest limits of sensitivity for the assay were 0.02 and 0.5 µg ml^{-1} in serum and urine, respectively. The day-to-day precision (coefficient of variation) ranged from 3.1 to 7.5% for the serum assay and from 2.8 to 4.3% for the urine assay.

Ofloxacin concentrations in serum were analyzed by a noncompartmental method (assuming $F = 1$) to obtain pharmacokinetic parameters. The areas under the concentration-time curve from 0 h (AUC_{0-t}) were determined by the trapezoidal rule. The extrapolation to infinity ($AUC_{0-\infty}$) was obtained by dividing the last measured concentration in serum by β, the slope of the terminal elimination phase of the curve that was determined by least-square linear regression on the terminal log-linear concentration decline. Then the half-life of elimination at β phase ($t_{1/2\beta}$), total body clearance (CL), and volume of distribution (V) were calculated by standard equations (4). Renal clearance (CL_R) was calculated from the unchanged urinary fraction and CL. Statistical comparisons of the pharmacokinetic parameters obtained after the single dose and at the steady state (last infusion) were performed by using the paired t test for AUC: $AUC_{0-\infty}$

TABLE 1. Pharmacokinetic parameters of i.v. infused ofloxacin (200 mg within 30 min) after either a single dose or the last infusion of nine doses every 12 h[a]

Determination after:	AUC (mg · h liter^{-1})[b]	$t_{1/2\beta}$ (h)	β (h^{-1})	CL (ml min^{-1})	V (liters)	CL$_R$ (ml min^{-1})
Single dose	14.02 ± 2.28	5.37 ± 0.83	0.132 ± 0.0198	241.06 ± 43.30	112.10 ± 22.80	157.80 ± 26.80
Last infusion	13.39 ± 2.22	4.76 ± 1.19	0.158 ± 0.049	278.30 ± 63.30	109.90 ± 15.10	143.30 ± 25.80

[a] Values are means ± standard deviation ($n = 8$).
[b] $AUC_{0-\infty}$ for the single dose and AUC_{0-12} for the last dose.

(single dose) versus AUC_{0-12} (steady state), CL, β, and V. Comparisons of multiple C_{min} values were performed by an analysis of variance followed by the "protected least significant difference Fisher test."

Mean concentrations of ofloxacin in serum after the single infusion decreased according to a biexponential curve with a rapid distribution phase followed by an elimination phase with a $t_{1/2\beta}$ of 5.37 ± 0.83 h, which was not modified in the last of the multiple infusions (Table 1). Mean ofloxacin concentrations reached 5.28 mg liter^{-1} at the end of the infusion and fell to 0.8 mg liter^{-1} at 4 h and 0.1 mg liter^{-1} after 24 h. No ofloxacin could be detected in any volunteer after 50 h (Fig. 1).

Ofloxacin was well distributed in the body at 112.0 ± 22.8 liters. V appeared not to be modified after the last administration. Total body clearance was 241.6 ± 43.3 ml min^{-1} at the first infusion and was not modified after the last infusion (Table 1).

Ofloxacin was mainly excreted by the kidneys, since the unchanged excreted fraction was 65.8 ± 8.4% of the administered dose, yielding an apparent CL$_R$ of 157.5 ml min^{-1} 1.73 m^{-2}. The CL$_R$ values were always higher than the CL$_{CR}$ of the subjects (Table 1). After multiple infusions of ofloxacin (200 mg twice a day), the C_{max} ranged from 4.0 to 4.49 mg ml^{-1}, whereas the C_{min} ranged from 0.34 to 0.56 mg ml^{-1}, and the plateau was reached immediately upon the second administration (no significant difference between the C_{min} values) (Fig. 1).

The data in the literature dealing with i.v. pharmacokinetics of ofloxacin in healthy volunteers are limited. Lode et al. (7) reported similar concentrations in plasma following a single i.v. dose of 200 mg, remaining above the mean MIC for 90% of the members of the family Enterobacteriaceae for

up to 4.5 h after administration. Our $AUC_{0-\infty}$ values after the single dose are also in agreement with those reported after an oral dose of 200 mg (3), indicating the good bioavailability of ofloxacin and allowing further comparison of the F-dependent pharmacokinetic parameters. Thus, the volume of distribution determined in our study (112.2 liters) was consistent with both that reported by Humbert et al. (G. Humbert, F. Borsa, W. Couet, J. B. Fourtillan, and M. Vincent du Laurier, Proc. 14th Int. Congr. Chemother., p. 23–24, 1985) and the CL reported by the same authors and by Lode et al. (7). In the same manner, the terminal half-life was in agreement with that reported by Lode et al. (7) (range, 4.26 to 7.8 h).

Within the first 6 h after administration of the single dose, mean concentrations of the drug in urine reached 259 mg liter^{-1}, indicating that ofloxacin is active in the urinary tract with this schedule.

When twice-daily oral doses were given for several days, Ichihara et al. (5) and Dragosa et al. (2) reported an accumulation factor of about 1.3, with an increase in the elimination half-life of about 20%, which could account for this observation (8). Our study was designed to evaluate, after repeated i.v. infusions, a possible modification of the main pharmacokinetic parameters which could yield an abnormal accumulation of ofloxacin. Our data demonstrate that the $AUC_{0-\infty}$ after the single infusion does not significantly differ from the AUC_{0-12} obtained after the last infusion (at steady state) and that the theoretical accumulation factor, calculated with a mean $t_{1/2\beta}$ of 5.37 h and a dosing interval of 12 h ($r = 1.28$), is even higher than the actual mean accumulation factor estimated by the AUC ratio ($r = 0.98 ± 0.23$). In addition, the observed C_{min} ± standard deviation remained within the range of the simulation (Fig. 1).
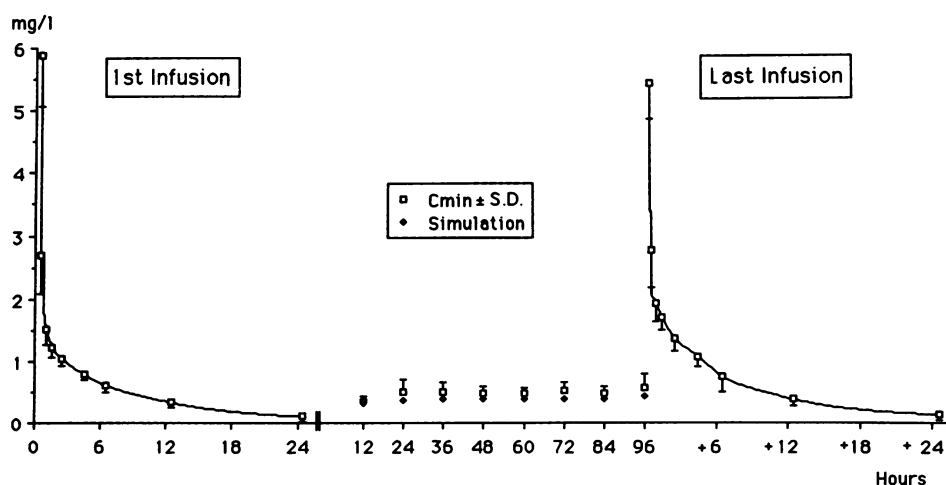

FIG. 1. Time profile of concentration in serum (mean ± standard deviation) of ofloxacin after the first and the last infusions (200 mg within 30 min) and trough levels in serum during repeated infusions (200 mg every 12 h).

We thus conclude that this dosing interval does not modify the pharmacokinetic profile of ofloxacin. If one compares the concentrations in serum obtained after i.v. infusion and oral intake of the same 200-mg dose of ofloxacin, it is seen that the C_{max} is approximately twofold higher at the end of the infusion (30 min) than 1 or 2 h after the oral dose (T_{max}). This point may be clinically relevant given the fact that the antibacterial effect of the fluoroquinolones is mainly concentration dependent. In this study, the i.v. formulation of ofloxacin was well tolerated (no side effects reported), and it appears that this parenteral presentation (alone or in combination with other antibiotics) may be useful in the initial therapy of severe infections caused by susceptible microorganisms. A 12-h dosing interval seems appropriate.

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