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Comparative Study of Pharmacokinetics of Two New Fluoroquinolones, Balofloxacin and Grepafloxacin, in Elderly Subjects

OSAMU KOZAWA,[1] TOSHIHIKO UEMATSU,[1]* HIROYUKI MATSUNO,[1] MASAYUKI NIWA,[1] SATORU NAGASHIMA,[2]† AND MITSUTAKA KANAMARU[3]

Department of Pharmacology, Gifu University School of Medicine, Gifu,[1] and Shitoro Clinic, Hamamatsu,[3] Japan, and Clinical Pharmacology Center, Georgetown University, Washington, D.C.[2]

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Comparative pharmacokinetics and tolerability were studied in healthy elderly volunteers for two new fluoroquinolones, balofloxacin (Q-35) and grepafloxacin (OPC-17116), the main excretion routes being the renal and hepatic routes, respectively. Both agents were well tolerated in elderly subjects. In comparison with previously reported data from healthy younger adults, the absorption of balofloxacin was slightly delayed and urinary excretion was delayed and diminished. As a significant linear correlation was observed between renal clearance of balofloxacin and creatinine clearance, the delayed and diminished urinary recovery was attributed to the reduced renal function of the elderly subjects enrolled in the study. The absorption of grepafloxacin was also delayed, and the maximum plasma drug concentration and area under the plasma drug concentration-time curve were increased in the elderly by 31 and 48%, respectively, over those in younger adults on the basis of dose normalized to body weight. The plasma terminal elimination half-life and urinary recovery remained unchanged. Decreases in distribution volume and total body clearance in the elderly were considered to be the primary factors contributing to these differences.

Fluorouinolone derivatives are widely prescribed to treat bacterial infections because they possess highly potent, broad-spectrum antibacterial activities and good tissue-penetrating ability (25). However, adverse effects on the central nervous system, phototoxicity, and potential drug interactions are major clinical concerns (2, 4, 8), even though the therapeutic value of fluoroquinolones is beyond question and outweighs such risks (18). To improve upon the safety, pharmacokinetic properties, and antibacterial activities and spectra, many new fluoroquinolones have been developed and are now undergoing clinical investigation (19, 25). Balofloxacin (Q-35) and grepafloxacin (OPC-17116) are two such new fluoroquinolones (5, 10–12, 27). These two drugs, however, exhibit quite different pharmacokinetic profiles. Balofloxacin is largely (70 to 80% of the dose) excreted via the urine as unchanged drug, whereas grepafloxacin is felt to be principally hepatically metabolized, since the urinary recovery of unchanged drug is only 10 to 13% (15–17).

The number of people aged 65 years and older is rapidly increasing worldwide. It is generally accepted that adverse drug effects are more frequently encountered in this age group. The heightened susceptibility to adverse reactions is due to a number of factors, including an increased incidence of disease, multiple-drug use, and altered pharmacokinetic properties of many drugs. In fact, it has been reported that the elderly compose 12% of the U.S. population but consume 33% of all prescription drugs, while the risk of drug interactions increases with the number of medications taken (20, 22, 28). It is also well recognized that many physiologic functions, including those of the gastrointestinal tract, kidneys, and liver, diminish with increasing age (6, 24). In consideration of these observations, full clarification of pharmacokinetic properties in the aged is essential for the safe application of newly developed drugs in this group.

In the present study the pharmacokinetics of balofloxacin and grepafloxacin were investigated in elderly subjects and compared with each other. Comparisons were also made between the data from the elderly subjects and previously obtained data from young subjects (15, 17). It is hoped that results of this study will be of use in the proper dosing of antimicrobial fluoroquinolones, any of which may be eliminated through either the renal or hepatic route or both.

MATERIALS AND METHODS

Subjects and study protocols. Elderly subjects were selected for enrollment in the study on the basis of physical examination, medical history, and clinical laboratory tests performed prior to drug administration and according to criteria such as being self-supporting and having no disease under treatment by long-term medication(s). All volunteers selected were stable and healthy, with no chronic disease. All but one subject were 65 years of age or more (this individual was 64.75 years old). Ten elderly subjects (three males and seven females) aged 71.8 ± 4.5 (mean ± standard deviation [SD]; range, 66 to 79) years and weighing 57.7 ± 10.9 kg and seven elderly female subjects aged 71.1 ± 4.6 (range, 64 to 78) years and weighing 52.0 ± 6.2 kg participated in the balofloxacin and grepafloxacin studies, respectively, after giving their written informed consent. Five female subjects participated in both studies with a washout interval of more than 1 year. Caffeine-containing beverages and smoking were prohibited from 12 h before until 24 h after drug administration. Use of other medications was restricted from 7 days before until 24 h after drug administration. Tolerability and pharmacokinetics were examined after a single oral dose of balofloxacin (200 mg) and multiple oral doses of grepafloxacin (200 mg once daily for 7 days).

Prior to the study, the experimental protocol had been reviewed and approved by the Ethics Committee of Shitoro Clinic, Shitoro, Hamamatsu, Japan.

In the single-dose study, balofloxacin was administered to the elderly volunteers after overnight (10-h) fasting. Venous blood samples (9 ml) were collected in heparinized tubes before (0 h) and 1, 2, 3, 4, 6, 8, 12, 24, and 32 h after drug administration. Urine was collected as voided just prior to drug administration (serving as an assay blank) and at intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, and 24 to 32 h after drug administration. In the multiple-dose study, grepafloxacin was administered to the elderly volunteers after overnight (10-h) fasting on the 1st, 4th, and 7th days and 0.5 h after breakfast on the other 4 days.

* Corresponding author. Mailing address: Department of Pharmacology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan. Phone: 81-58-267-2231. Fax: 81-58-267-2959. Electronic mail address: uematsu@cc.gifu-u.ac.jp.

† Present address: Shitoro Clinic, Hamamatsu 432, Japan.

Blood samples (3 ml) were collected prior to each drug administration and 1, 2, 3, 4, 8, and 12 h after the first, fourth, and seventh (last) dose administrations. Additional samples were collected 24, 48, and 72 h after the seventh dose. Urine was collected as voided just prior to administration (serving as an assay blank) and during each 24-h period up until 72 h after the seventh dose administration.

Plasma was immediately separated by centrifugation at 2,000 × *g* for 10 min and stored at −20°C until analyzed. The urine collected during each time period was mixed well and weighed, and an aliquot (7 to 10 ml) was stored at −20°C until analyzed.

All subjective and objective symptoms observed by the investigators, or reported by the subjects either spontaneously or in response to a direct question, were noted. If any adverse experience occurred after administration of each test drug, the subject was to be given appropriate treatment and close medical supervision. The casualty and severity ratings of any clinical adverse experiences were evaluated.

Blood biochemistry and hematology tests and urinalysis were performed at the screening visit and immediately before and 24 h after dosing in the single-dose balofloxacin study. In the multiple-dose grepafloxacin study these tests were performed at the screening visit, immediately before the first and fourth dose administrations, and 24 h following the last dose administration. Electrocardiograms were obtained prior to and 24 h following the single-dose administration of balofloxacin as well as prior to and 2 h following each of the first, fourth, and seventh (last) doses of grepafloxacin and 24 h following the last grepafloxacin dose. Vital signs were monitored immediately before and periodically up until 24 h after dose administrations.

Analytical methods. Plasma and urinary balofloxacin and grepafloxacin concentrations were quantitated by reversed-phase high-performance liquid chromatography (HPLC) according to previously reported methods (14, 26).

Balofloxacin was measured by HPLC using a Shimadzu (Kyoto, Japan) HPLC system composed of a pump (LC-9A), an autosampler (SIL-6B), and a system controller (Chromatopac C-R6A) together with a fluorescence spectrophotometer (F-1000; Hitachi, Tokyo, Japan; excitation and detection wavelengths: 295 and 500 nm). An octyldecyl silane analytical column (AM-301-3; YMC, Kyoto, Japan) was used. The mobile phase was a mixture of water, acetonitrile, and triethylamine (81:19:1, vol/vol), adjusted to pH 4.5 by adding phosphoric acid. The solution was filtered through a membrane filter (pore size: 0.45 μm) and degassed before use. The HPLC system was operated at ambient temperature, and the flow rate was 1.0 ml/min. Plasma and urine were diluted 1:10 and 1:100, respectively, with 100 mM phosphate buffer (pH 7.0). Q36, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-aminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid (0.5 μg/ml), used as an internal standard, and 5 ml of dichloromethane were successively added to an aliquot (0.1 ml) of the diluted sample. The mixture was agitated for 10 min on a shaker and centrifuged at 1,700 × *g* for 5 min. The organic layer was transferred and evaporated under a stream of nitrogen gas at 40°C in a water bath. The residue was dissolved in 0.1 ml of the mobile phase, and aliquots (20 μl) were injected onto the HPLC. The calibration curve was generated by measuring the control solutions adjusted to concentrations of 10, 50, 100, 500, and 1,000 ng of balofloxacin per ml. The calibration curve thus obtained was linear within this concentration range ($r = 0.999$). The intraday ($n = 3$) and interday ($n = 7$) precisions determined at concentrations of 50 and 500 ng/ml were 12.2 and 2.2% and 3.2 and 1.8%, respectively, as expressed as the coefficient of variation. Therefore, the detection limit was considered to be below 10 ng/ml.

Grepafloxacin was also measured by HPLC. The HPLC system was composed of a pump (Waters model 510; Nihon Millipore, Tokyo, Japan), an autosampler (WISP719B; Nihon Millipore), and a system controller (Chromatopac C-R6A; Shimadzu) together with a fluorescence spectrophotometer (RF-535; Shimadzu; excitation and detection wavelengths: 285 and 448 nm). A TSK gel ODS-80TM analytical column (Tohso, Tokyo, Japan) was used. The mobile phase was a mixture (27:73, vol/vol) of acetonitrile and 0.1% (vol/vol) H_3PO_4 in a 20 mM solution of Na_2SO_4. The solution was filtered through a membrane filter (pore size: 0.45 μm) and degassed before use. The HPLC system was operated at ambient temperature, and the flow rate was 0.8 ml/min. OPC-17203, (±)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-5-ethyl-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (100 ng), used as an internal standard; 1 ml of 25 mM phosphate buffer (pH 6.9); and 5 ml of chloroform were successively added to an aliquot (0.2 ml) of plasma or urine. The mixture was agitated on a shaker and centrifuged at 1,700 × *g* for 10 min. The organic layer (3.5 ml) was transferred and evaporated under a stream of nitrogen gas at 40°C in a water bath. The residue was dissolved in 1 ml of the mobile phase, and aliquots (10 to 25 μl) were injected onto the HPLC. The calibration curve was generated by measuring the control solutions adjusted to grepafloxacin concentrations of 25, 50, 100, 500, 1,000, 2,500, and 5,000 ng/ml and 0.25, 0.5, 1, 2.5, 5, 10, 25, and 50 μg/ml for plasma and urine, respectively. The calibration curve thus obtained was linear within these concentration ranges ($r = 0.999$). The intraday precision ($n = 5$) determined at the above-mentioned concentrations was 1.5 to 4.0% as expressed as the coefficient of variation. Therefore, the detection limit was considered to be below 25 and 250 ng/ml for plasma and urine, respectively.

Pharmacokinetic analysis. In previous phase I studies using younger healthy subjects (15–17), the concentrations of both fluoroquinlones in plasma were satisfactorily fitted to a two-compartment open model with first-order oral absorption. For comparison, the plasma drug concentration-versus-time data for each subject in the current study were individually fitted to this model by employing a nonlinear least-squares computer program (Multi) (29). The data apparently fitted better to a two-compartment model than to a one-compartment model with a lower Akaike's information criterion value. The apparent steady-state volume of distribution (V_{ss}/F) was calculated by using the distribution volume of the central compartment (V_c) and two intercompartmental microconstants (k_{12} and k_{21}) as follows: $V_{ss}/F = (V_c/F) \times [1 + (k_{12}/k_{21})]$. In order to compare elimination half-life ($t_{1/2\beta}$) of grepafloxacin among the first, fourth, and seventh (last) doses, the terminal-phase rate constant was also calculated as the slope of the least-squares regression line for log-transformed *n*-terminal datum points, which ($n \geq 3$) were selected to minimize the mean-square error term for the regression. The maximum concentration in plasma (C_{max}) and the time to reach C_{max} (T_{max}) were obtained by visual inspection. The area under the plasma drug concentration-versus-time curve during 24 h after administration (AUC_{0-24}) was calculated by use of the trapezoidal rule. The $AUC_{0-\infty}$ was also calculated by use of the trapezoidal rule until the time of the last quantifiable plasma drug concentration and then to infinity by using the quotient of the last measurable concentration to the terminal-phase rate constant, which was calculated by the above-mentioned curve fitting (21). Renal clearance (CL_R) was calculated by dividing the amount of drug excreted into the urine by the AUC. Creatinine clearance (CL_{CR}) was determined by dividing the amount of creatinine excreted into the urine in the 12 h prior to drug administration by the serum creatinine concentration.

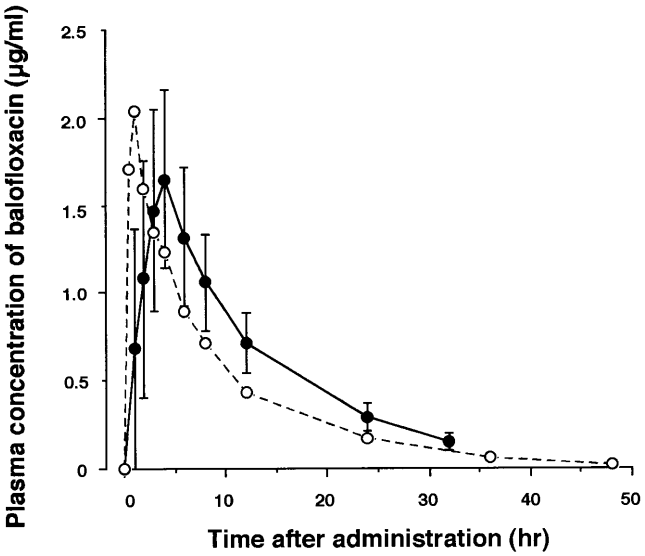

FIG. 1. Plasma balofloxacin concentration-versus-time profile after single oral administration of 200 mg in elderly volunteers (●). Symbols and bars represent means ± SDs ($n = 10$). The mean plasma drug concentration-versus-time profile determined in healthy younger adults at the same dose level (○) is also illustrated for reference (15).

Statistics. Means of the pharmacokinetic parameters were compared between the younger and elderly groups. The significance of difference was tested by either Student's *t* test or Cochran-Cox's method, depending on whether variances of parametric data were equal between both groups, or Wilcoxon's U test for nonparametric data such as T_{max}.

RESULTS

Clinical results. Balofloxacin and grepafloxacin were well tolerated by the subjects. No adverse clinical effects were noted, and none of the subjects developed any laboratory abnormalities.

Pharmacokinetic results. Figures 1 and 2 illustrate the profiles of the balofloxacin concentration in plasma and of the urinary recovery of unchanged drug, respectively, as a function of time following oral administration of 200 mg, the clinically expected dose in the elderly. The pharmacokinetic parameters are shown in Table 1. Compared with the parameters determined in younger adults (15), statistically significant age-related effects were found for T_{max}, $AUC_{0-\infty}$, and urinary recovery within the first 24 h: T_{max} was prolonged, $AUC_{0-\infty}$ was

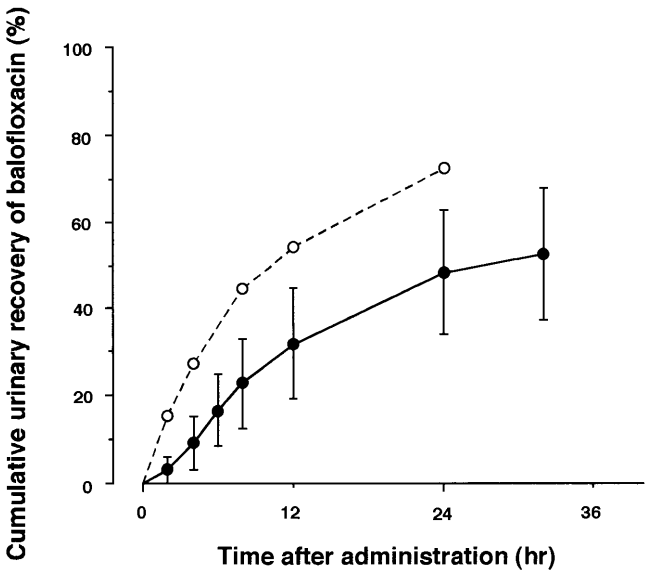

FIG. 2. Cumulative urinary recovery of balofloxacin expressed as a percentage of the administered dose (200 mg orally) in elderly volunteers (●). Symbols and bars represent means ± SDs (n = 10). The mean urinary recovery determined in healthy younger adults at the same dose level (○) is also illustrated for reference (15).

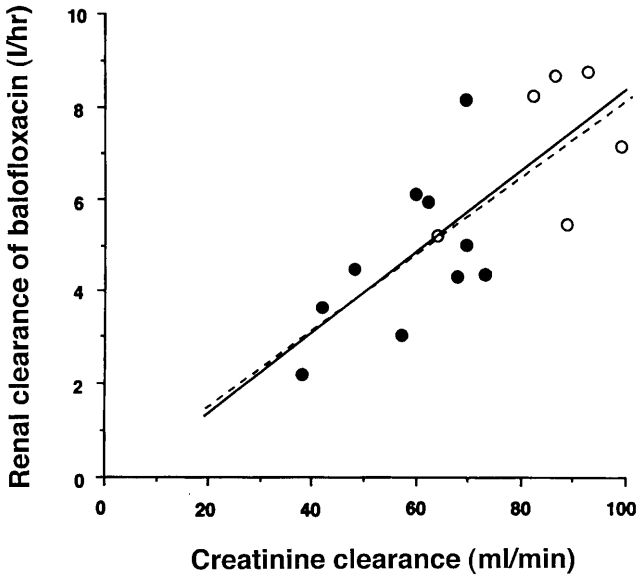

FIG. 3. Relationship between CL_R of balofloxacin and CL_{CR}. Correlation analysis was performed using the data from the present study in elderly volunteers alone (● and solid line) (r = 0.629; n = 10; $P < 0.05$) and in combination with unpublished data obtained in a multiple-dose balofloxacin study (300 mg twice a day for 6.5 days) using six healthy younger male adults (○ and broken line) (r = 0.754; n = 16; $P < 0.001$).

increased, and urinary recovery was diminished. C_{max} was decreased, though not significantly. The apparent total body clearance (CL/F) and CL_R were significantly diminished in elderly subjects. Significant positive correlation was observed between CL_R of balofloxacin and CL_{CR} (Fig. 3) ($y = -0.106 + 0.0820x$; r = 0.629; n = 10; $P < 0.05$). When unpublished data obtained in a multiple-dose study (300 mg twice a day for 6.5 days) using six healthy younger male adults were combined with the data of the present study and reanalyzed, a more significant linear correlation was observed ($y = -0.220 + 0.0853x$; r = 0.754; n = 16; $P < 0.001$). In both cases of regression analysis the 95% confidence interval for the estimate of intercept included zero.

Figures 4 and 5 illustrate the profiles of the grepafloxacin concentration in plasma and of the urinary recovery of unchanged drug, respectively, as a function of time following multiple-oral-dose administration at the clinically expected dosage regimen (200 mg once daily) for the elderly. The pharmacokinetic parameters are also described in Table 1. Compared with parameters derived in younger adults (17), statistically significant age-related effects were found for T_{max} of days 1 and 7; C_{max}, AUC_{0-24}, CL/F, and CL_R of days 1, 4, and 7; and V_{ss}/F: T_{max} was prolonged, C_{max} and AUC_{0-24} were increased, and V_{ss}/F was decreased, whereas terminal disposition half-life and urinary recovery remained unchanged. CL_R was signifi-

TABLE 1. Pharmacokinetic parameters of balofloxacin and grepafloxacin in the elderly[a]

Group	n	Body wt (kg)	T_{max} (h)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	AUC_{0-24} (μg · h/ml)	CL/F (liters/h)	CL_R (liters/h)	V_{ss}/F (liters)	$t_{1/2\beta}$ (h)
Balofloxacin[b]										
Elderly	10	57.7 ± 10.9	3.7 ± 1.3[c]	1.72 ± 0.50	22.9 ± 5.0[d]		8.12 ± 2.47[c]	4.73 ± 1.69[c]	49.9 ± 45.2	13.3 ± 6.2
Young[e]	6	66.0 ± 8.8	1.1 ± 0.5	2.17 ± 0.36	17.1 ± 1.8		11.80 ± 1.16	9.47 ± 1.78	38.3 ± 21.1	7.8 ± 1.2
Grepafloxacin										
Day 1										
Elderly	7	52.0 ± 6.2[c]	3.3 ± 0.5[c]	1.40 ± 0.40[c]		17.15 ± 4.39[c]	9.97 ± 3.44[c]	0.98 ± 0.51[c]		10.2 ± 1.2
Young[f]	6	65.5 ± 8.0	1.8 ± 0.7	0.82 ± 0.07		8.09 ± 1.04	20.94 ± 3.41	2.38 ± 0.72		9.2 ± 1.6
Day 4										
Elderly	7		3.1 ± 1.1	1.89 ± 0.44[c]		23.46 ± 6.08[c]	9.09 ± 2.57[c]	1.33 ± 0.26[c]		10.9 ± 1.7
Young[f]	6		2.8 ± 0.8	0.96 ± 0.08		11.71 ± 1.33	17.28 ± 2.09	2.18 ± 0.19		9.4 ± 1.2
Day 7										
Elderly	7		3.1 ± 0.7[d]	1.65 ± 0.33[c]		22.54 ± 5.25[c]	9.33 ± 2.31[c]	1.42 ± 0.21[c]		12.0 ± 1.6
Young[f]	6		2.0 ± 0.8	0.99 ± 0.09		12.05 ± 1.16	16.73 ± 1.68	2.36 ± 0.20		10.1 ± 1.7
Days 1–9[b]										
Elderly	7						9.45 ± 2.72[c]		172.7 ± 50.3[c]	15.9 ± 2.4
Young[f]	6						18.05 ± 1.83		314.1 ± 55.0	15.5 ± 3.1

[a] Values are expressed as means ± SDs. Significance of difference was tested by Student's t test by Cochran-Cox's method, or by Wilcoxon's U test, where appropriate.
[b] All data of plasma drug concentration are analyzed together by fitting them to a 2-compartment open model.
[c] $P < 0.01$, elderly versus young.
[d] $P < 0.05$, elderly versus young.
[e] Reference 15. (Data are normalized to a daily dose of 200 mg with the assumption of linear pharmacokinetics.)
[f] Reference 17. (Data are normalized to a daily dose of 200 mg with the assumption of linear pharmacokinetics.)

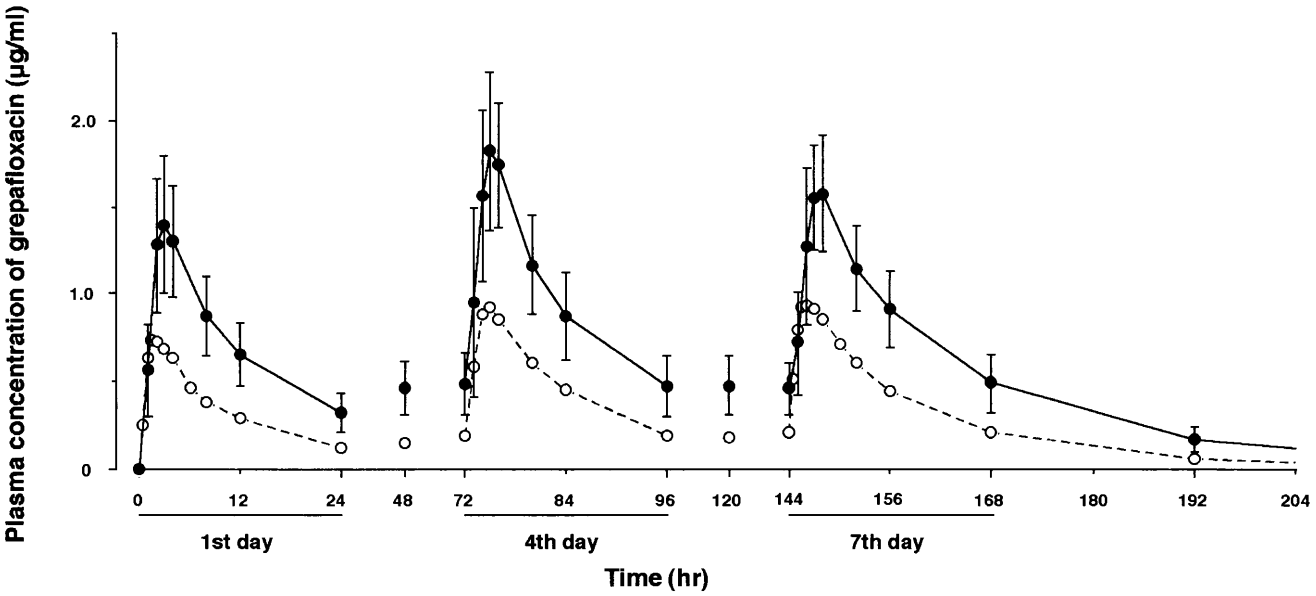

FIG. 4. Plasma grepafloxacin concentration-versus-time profile after multiple oral administration (200 mg once daily for 7 days) in elderly volunteers (●). Symbols and bars represent means ± SDs ($n = 7$). The mean plasma drug concentration-versus-time profile determined in healthy younger adults in a regimen of 300 mg once daily for 7 days (○) is also illustrated for reference after being normalized to a daily dose of 200 mg with the assumption of linear pharmacokinetics (17).

cantly decreased in elderly subjects compared with that of younger subjects. When weight-normalized CL/*F* and CL_R were also calculated and compared since body weight was significantly different between both groups (Table 1), statistically significant differences were still observed. Since CL_{CR} was measured in elderly subjects on days 4 and 7, the correlation of CL_R with CL_{CR} was analyzed for both time points. At either time point, however, no significant correlation was observed (day 4, $r = 0.459$; day 7, $r = 0.609$, $n = 7$).

DISCUSSION

Results of our study demonstrate the following pharmacokinetic properties of the two new fluoroquinolones in elderly subjects compared with those in younger adults. The absorption of these fluoroquinolones was slightly delayed. Plasma elimination of balofloxacin, which principally occurs via renal excretion, was prolonged, and concentrations in plasma of grepafloxacin, which is mainly eliminated through hepatic bio-

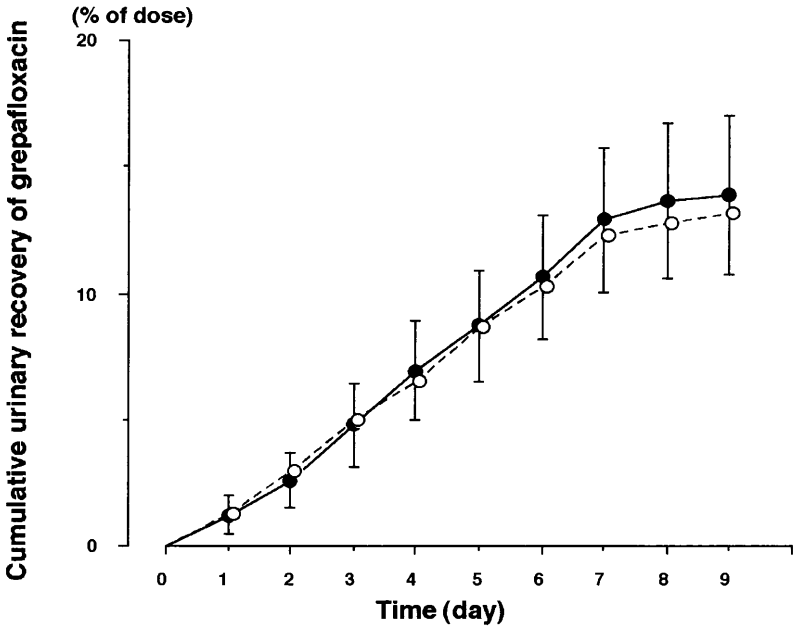

FIG. 5. Cumulative urinary recovery of grepafloxacin expressed as a percentage of the total administered dose in elderly volunteers (●). Symbols and bars represent means ± SDs ($n = 7$). The mean urinary recovery determined in healthy young adults as described in the legend to Fig. 4 (○) is also illustrated for reference (17).

transformation, were elevated. However, both drugs were well tolerated in regimens using clinically relevant doses.

It is well-known that age affects the distribution and elimination of many drugs because of physiological changes associated with aging. Organ functions in the elderly generally decline as a result of advancing age. For example, cardiac output decreases by 30 to 40% between the ages of 25 and 65 years, and the glomerular filtration rate as expressed by CL_{CR} declines progressively with age. Body composition also changes with aging. Total body water and lean body mass are lower in the elderly, both in absolute terms and as percentages of body weight. The decrease in the proportion of lean body mass per unit of body weight has been shown to alter the distribution volumes of various drugs (7). In the case of ciprofloxacin, increases of about twofold in C_{max}, AUC, and terminal disposition half-life were reported after oral administration in elderly subjects compared with those in younger subjects (1, 17). These findings show that the clearance of ciprofloxacin is reduced in the elderly, while the volume of distribution is also simultaneously reduced, probably because of the decrease in lean body mass per unit of total body weight. On the other hand, Shah et al. (23) reported increases of less than twofold in C_{max}, AUC, and $t_{1/2\beta}$ in elderly subjects after intravenous infusion of ciprofloxacin and, in addition, a significant correlation between the CL_R of ciprofloxacin and CL_{CR}, concluding that the reduced first-pass metabolism following oral administration in the elderly may add to the effects of the lower CL_{CR} and lower distribution volume.

In light of the above-mentioned age-related physiological changes and observations on ciprofloxacin, the results of the present study can be interpreted as the absorption of both fluoroquinolones being retarded in the elderly probably because of decreased gastrointestinal motility (9). As a significant linear correlation was observed between the CL_R of balofloxacin and CL_{CR}, the retarded and diminished urinary recovery of balofloxacin determined in the present study was mainly attributable to the lowered renal function of the elderly subjects enrolled in the study. C_{max} and AUC of grepafloxacin were increased in the elderly, as shown in Table 1, compared with historic data, which were normalized to dose of 200 mg with the assumption of linear pharmacokinetics, in healthy younger controls. Since there was a statistically significant difference in body weight between the two groups, both parameters were compared on a weight-normalized basis, showing that C_{max} and AUC were still greater in the elderly (31 and 48%, respectively). Since grepafloxacin is highly lipid soluble and has a higher penetration into tissues (5), the above finding is attributable to the decreases in both distribution volume, perhaps as a result of the decreased amount of fat per unit of body weight in the elderly, and total body clearance. Therefore, a reduction of dosage should be recommended in the elderly, although the safety margin of grepafloxacin is sufficiently large (17). CL_R of grepafloxacin was significantly reduced in elderly subjects probably because of the reduced renal function, as in the case of balofloxacin. However, since the urinary recovery was at most about 13% of the given dose and almost the same in both age groups and the $t_{1/2\beta}$ remained unchanged, there should be no need for adjusting dosage of grepafloxacin according only to individual renal function.

There may exist additional differences in pharmacokinetic properties related to gender. In the multiple-dose study of grepafloxacin, the elderly volunteers were exclusively female, and this might have produced some bias in the pharmacokinetic parameters obtained. In the case of ciprofloxacin, however, Shah et al. (23) reported that the apparent differences in C_{max} and AUC between males and females were due to the difference in body weight between the two groups. Although further study is needed to clarify whether gender differences exist, if any do exist, they are probably small.

In conclusion, when prescribing a fluoroquinolone for an elderly patient, precautions should be taken with regard to age-related changes in pharmacokinetic properties.

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