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Pharmacokinetics of Sparfloxacin in Patients with Renal Impairment

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The pharmacokinetics of sparfloxacin were studied in 14 renal failure patients (group I, 7 with creatinine clearance of >10 to 30 ml/min; and group II, 7 with creatinine clearance of ≤10 ml/min) after a single oral dose of 400 mg. Plasma and urine samples were collected up to 144 h postdosing for determination of parent and total (parent-plus-glucuronide-conjugated) sparfloxacin levels, by high-pressure liquid chromatography assay and UV detection. The elimination of the drug in patients compared with that in healthy volunteers was markedly impaired. The mean elimination half-lives of sparfloxacin were 34.9 and 38.5 h in group I and group II, respectively, versus 19.1 h in healthy volunteers. Conjugated drug half-lives were 23.7, 35.0, and 15.3 h, respectively. The renal clearance of the drug was markedly reduced in the patients, with values of 6.8, 4.8, and 21.2 ml/min determined for group I, group II, and healthy subjects, respectively, for parent sparfloxacin and with values of 31.5, 14.0, and 327 ml/min for conjugated sparfloxacin. The nonrenal clearance of sparfloxacin was moderately, but not significantly, decreased in group II renal failure patients. No difference between the two groups of patients was detected in sparfloxacin levels in plasma. A significant relationship between pharmacokinetic parameters and creatinine clearance was observed only for renal clearance of parent or conjugated sparfloxacin.

A large number of fluorinated 4-quinolones has been developed in recent years. While there are differences in the details of their antimicrobial activity, they are all much more active in vitro than earlier 4-quinolone compounds. Most exhibit the greatest activity against aerobic gram-negative organisms and are generally less active against staphylococci, streptococci, and anaerobia. Sparfloxacin [5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid; AT-4140; RP 64206] is a new quinolone with broad antibacterial activity. It is more active than ciprofloxacin against staphylococci, streptococci, and enterococci. Sparfloxacin is more active than ciprofloxacin against isolates in the *Bacteroides fragilis* group and against clostridia. On the other hand, sparfloxacin is less active than ciprofloxacin against members of the family *Enterobacteriaceae* or against *Pseudomonas aeruginosa* (1, 6, 7, 13).

Studies of young subjects with normal renal function have shown that sparfloxacin kinetics are mainly characterized by a long elimination half-life ($t_{1/2}$) of 16 to 20 h (5, 10), low protein binding (45%) (9), and sole transformation into one inactive glucuronide conjugate (12). The elimination is mainly nonrenal, since parent and conjugated drug urinary excretions account for approximately 30% of the dose. The purpose of the present study was to investigate the pharmacokinetics of sparfloxacin in cases of renal insufficiency after a single oral dose of 400 mg.

MATERIALS AND METHODS

Fourteen subjects with chronic renal impairment were included in the study, which was approved by the Ethical Committee of the University of Rouen, Rouen, France. They gave written consent to participate after the aim of the trial was explained to them. It was determined that the subjects were in good health, with the exception of their renal impairment, on the basis of physical examination, medical history, and laboratory tests. Their creatinine clearance (CL_{CR}) had been stable during the previous 6 months, as assessed by their selection creatinine levels within ±40 μmol/ml. Subjects with a history of allergy to drugs and subjects with hepatic disease or unstable or decompensated pulmonary, cardiovascular, gastrointestinal, or oncologic disease were excluded. A positive hepatitis B or human immunodeficiency virus test, any antibiotic treatment within 1 month of the study, or pregnancy excluded the subject from this study. All previously prescribed concurrent medication, except barbiturates, phenytoin, antacids, and calcium salts was continued throughout the study. The control group consisted of six healthy subjects chosen by lot from a separate single-rising-dose sparfloxacin pharmacokinetic study (10). The data from these subjects were generated in the same laboratory, with the same analytical and pharmacokinetic methods.

The demographic characteristics of the subjects are shown in Table 1. The patients were divided into two groups on the basis of glomerular filtration rate, as determined by endogenous CL_{CR}, which was measured for a 24-h urine period and corrected for 1.73 m^2 of body surface area. Group I included seven patients, with CL_{CR} of >10 to 30 ml/min per 1.73 m^2 of body surface, and group II included seven patients with CL_{CR} ranging between 2 and 10 ml/min per 1.73 m^2 of body surface. Group III consisted of six healthy subjects whose CL_{CR} was estimated to be between 75 and 133 ml/min per 1.73 m^2 of body surface area. CL_{CR} in these subjects was estimated from their creatinine level in serum by the Cockroft equation (2).

A physical examination and medical history, complete blood count, platelet count, standard serum chemistry panel, and 12-lead electrocardiogram were performed a maximum of 2 weeks before the study. The physical examination, medical history, and laboratory tests were repeated on day 7 after administration. All participants were admitted to the hospital

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TABLE 1. Mean demographic data for subjects in this study

Parameter	Mean ± SD for group[a]		
	I	II	III
Age (yr)	55 ± 10 (52–69)	56 ± 17 (20–72)	23 ± 3 (20–28)
CL_{CR} (ml/min/1.73 m^2)	22.0 ± 6.3	7.7 ± 2.4	108 ± 16[b]
Creatinine (μM) at inclusion	437.6 ± 215.8	662.3 ± 164.5	95 ± 10
Gender, M/F[c]	4/3	5/2	6/0
Ht (cm)	166 ± 11 (156–180)	165 ± 9 (158–181)	180 ± 6 (171–187)
Wt (kg)	70 ± 11 (57–90)	69 ± 12 (57–90)	69 ± 8 (71–83)

[a] Ranges are indicated in parentheses.
[b] Estimated by equation of Cockroft.
[c] M, male; F, female.

at least 24 h before drug administration. During that period, a baseline 24-h urine collection was obtained for CL_{CR} determination. An absolute fast, water excepted, was maintained from midnight until 6 h after drug administration. Each patient received a single oral 400-mg dose of sparfloxacin administered as four 100-mg tablets with 100 ml of water.

Blood samples (5 ml), for the renal impairment patients, were collected in heparinized tubes at the following times: before and 1, 2, 3, 4, 6, 8, 12, 24, 34, 48, 72, 96, and 144 h after drug administration. For the healthy subjects, blood samples (6 ml) were collected before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 h after drug administration. All the samples were immediately centrifuged at 1,000 × *g* for 10 min at 4°C, and three plasma aliquots were stored at −20°C until assayed for sparfloxacin and glucuronide conjugate. Urine samples from renal impairment patients were obtained before and at intervals of 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h after drug administration. From healthy subjects, urine was collected over the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h after dosing. During the collection periods, the volume was measured and 10-ml aliquots were stored at −20°C until assayed for sparfloxacin and glucuronide conjugate.

Clinical laboratory studies were performed before sparfloxacin administration and at the end of the study. Subjects were closely observed for signs and symptoms of drug intolerance.

Analytical method. The concentrations of sparfloxacin in plasma and urine were determined by reverse-phase high-pressure liquid chromatography (HPLC) and UV detection for all the subjects. A semi-automated solid-phase extraction method was used to extract sparfloxacin from plasma before HPLC, whereas diluted urine samples were injected directly into the chromatograph. Since sparfloxacin glucuronide was not available as a reference standard, conjugated-drug level was determined as total minus free-drug level, where total drug level expressed the sparfloxacin level after alkaline hydrolysis of the sample.

Plasma was centrifuged for 10 min at 1,000 × *g* at room temperature before extraction. Plasma (0.5 ml) spiked with 50 μl of internal standard [RP 41983 or 1-ethyl-6-chloro-1-4,dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid at 20 μg/ml] was placed on an AASP cassette (Varian, Walnut Creek, Calif.), with an AASP prep station (rinsed before use with methanol). Washing was done with water, and elution of drugs from the cassette cartridges was performed with the HPLC mobile phase. Sparfloxacin and the internal standard were analyzed with a reverse-phase column (Asahi PAK OD1, 50; 150 by 6 mm) with UV detection at 364 nm. The mobile phase consisted of 5% methanol-acetonitrile-acetic acid (11.6/11.6/76.8, vol/vol/vol). The procedure has been shown to have a mean intraassay coefficient of variation of 4.8 to 3.7% over the concentration range of 25 to 2,000 ng/ml. The

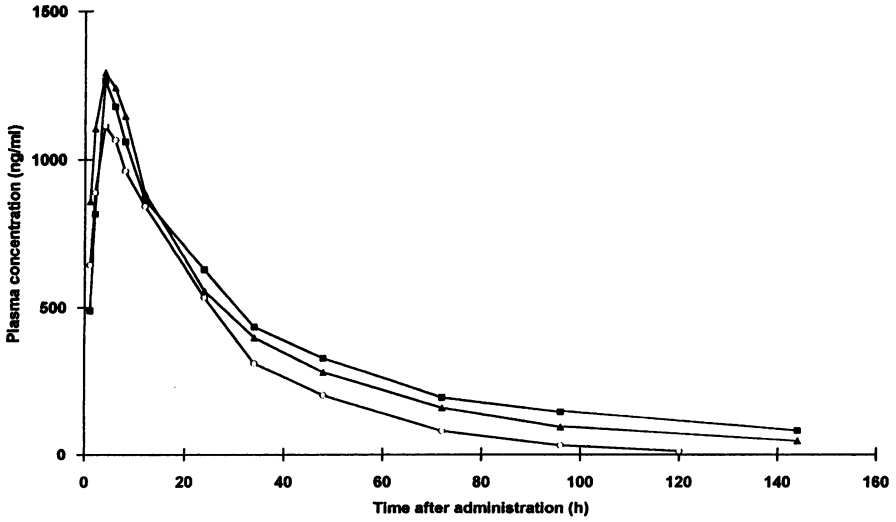

FIG. 1. Mean sparfloxacin concentrations in plasma of group I patients (▲), group II patients (■), and healthy subjects (○). A single 400-mg dose of sparfloxacin was administered.

TABLE 2. Mean pharmacokinetic parameters of parent sparfloxacin following oral administration of 400 mg of sparfloxacin[a]

Group	C_{max} (ng/ml)	T_{max} (h) median[b]	AUC_{144h} (ng · h/ml)	AUC_{inf} (ng · h/ml)	$t_{1/2}$ (h)	CL_P (ml/min)	Urinary excretion (% of dose)	CL_R (ml/min)	CL_{NR} (ml/min)
I (n = 7)	1,426 ± 645	4 (1–8)	41,680 ± 18,956	44,240 ± 19,173	34.9[c] ± 9.2	176 ± 72	4.04[c] ± 1.91	6.8[c] ± 2.3	169 ± 72
II (n = 7)	1,313 ± 436	4 (4–8)	45,336 ± 10,307	49,387 ± 11,101	38.5[c] ± 13.4	141 ± 31	3.19[c] ± 0.94	4.8[c] ± 1.3	136 ± 31
III (n = 6)	1,094 ± 234	5 (3–6)	NA[d]	31,458 ± 5,874	19.1 ± 2.5	218 ± 42	9.70 ± 2.26	21.2 ± 3.3	197 ± 42

[a] Parameters given are mean values ± standard deviations. CL_{NR}, nonrenal clearance.
[b] Ranges are indicated in parentheses.
[c] Significantly different from healthy subjects ($P < 0.05$).
[d] NA, not available.

interassay coefficient of variation was below 8% for concentrations of both 1,000 and 50 ng/ml. Urine samples were supplemented with internal standard and analyzed without further processing. Total (parent-plus-conjugated) sparfloxacin was measured by the same procedures after alkaline hydrolysis (10 min with 1 N NaOH) of the main metabolite, sparfloxacin acylglucuronide. This last process has been found suitable to ensure complete hydrolysis of the drug conjugate. Calibration curves of the drug in plasma typically comprised six standards with concentrations ranging from 25 to 2,000 ng/ml and 500 to 10,000 ng/ml in urine. The mean calibration curve correlation coefficients were always higher than 0.999. The quantification limits were 25 ng/ml in plasma and 500 ng/ml in urine for the renal impairment patients and 15 and 250 ng/ml, respectively, in plasma and urine for healthy subjects.

Pharmacokinetic analysis. Concentration-time data for parent sparfloxacin in plasma were interpreted by a noncompartmental approach, and the following pharmacokinetic parameters were computed (16) with the APIS program (4): maximal level in plasma (C_{max}), time to maximal level in plasma (T_{max}), and apparent elimination half-life ($t_{1/2}$) estimated by semilog linear regression of the terminal concentration-time data. Area under the plasma level-versus-time curve (AUC_t and AUC_{inf}) was calculated by the trapezoidal rule (3), from time 0 to time t, last time of quantification. AUC_{inf}, extrapolated to infinity, was calculated as $AUC_t \times C(t)/k_e$, where t is the last time of quantification and k_e is the elimination rate constant estimated by log-linear regression of the terminal curve, $C = f(t)$. The apparent clearance in plasma (CL_P) was calculated as follows: dose/AUC_{inf} (assuming complete bioavailability).

The amount of parent drug excreted in each urinary fraction was used to compute the cumulative amounts excreted following the single-dose administration of sparfloxacin. The renal clearance was calculated as $CL_R = A_{et}/AUC_t$, where A_{et} is the amount of drug excreted in urine over 0 to 120 h.

Total sparfloxacin was measured in plasma after alkaline hydrolysis. The conjugated sparfloxacin levels were calculated as total sparfloxacin minus parent sparfloxacin. Since sparfloxacin is metabolized only to an acylglucuronide conjugate in humans, it is assumed that (total sparfloxacin-minus-parent sparfloxacin) levels represent levels of sparfloxacin which are conjugated with glucuronic acid. The following pharmacokinetic data were computed with the results for conjugated sparfloxacin: C_{max}, T_{max}, AUC_t, and AUC_{inf}.

Total sparfloxacin was measured after alkaline hydrolysis of the urinary samples from all the subjects. As for plasma, it is assumed that (total sparfloxacin-minus-parent sparfloxacin) levels represent levels of sparfloxacin which are conjugated with glucuronic acid. The CL_R was calculated as $CL_R = A_{et}/AUC_t$, where A_{et} is the amount of drug excreted in urine over 0 to t h (t being the last quantification time for the renal impairment patients and 48 h for the healthy subjects, because after 48 h, only traces of sparfloxacin were detected in healthy subjects' urine).

Statistical analysis. All results are expressed as means ± standard deviations, except T_{max} values, which are expressed as median and range. Continuous variables C_{max}, AUC, $t_{1/2}$, and clearance were analyzed by using the General Linear Model procedure from SAS software (15) and then a Tukey test for comparison. T_{max} was analyzed by a rank procedure and General Linear Model on ranks. A comparison was effected between the three groups: group I renal impairment patients, group II renal impairment patients, and healthy subjects.

Correlations between pharmacokinetic parameters of sparfloxacin (AUC, CL_P, CL_R, nonrenal clearance, $t_{1/2}$) and CL_{CR} of the renally impaired patients were determined by linear regression analysis. For the metabolite pharmacokinetic data, only AUC and CL_R versus CL_{CR} correlations were studied. Only significant correlations are presented.

RESULTS

Clinical results. Sparfloxacin was very well tolerated by volunteers and uremic patients. No adverse clinical effect was noted, and no patients developed any biological abnormality.

Pharmacokinetic results. Mean levels of sparfloxacin in plasma after a single oral dose of 400 mg, from healthy subjects and group I and II patients, are illustrated in Fig. 1. Mean pharmacokinetic parameters are provided in Table 2.

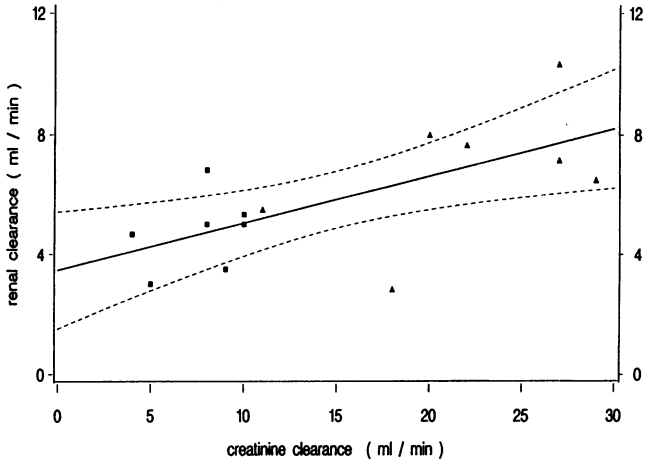

FIG. 2. Sparfloxacin clearance versus CL_{CR} in group I patients (▲) and group II patients (■). The subjects were given a 400-mg oral dose of sparfloxacin. The regression equation found is as follows: $CL_R = 0.0095\ CL_{CR} + 0.2078$; $r^2 = 0.43$, $r = 0.66$, $P > F = 0.0107$. The 95% confidence limit for the mean is indicated by the dashed lines.

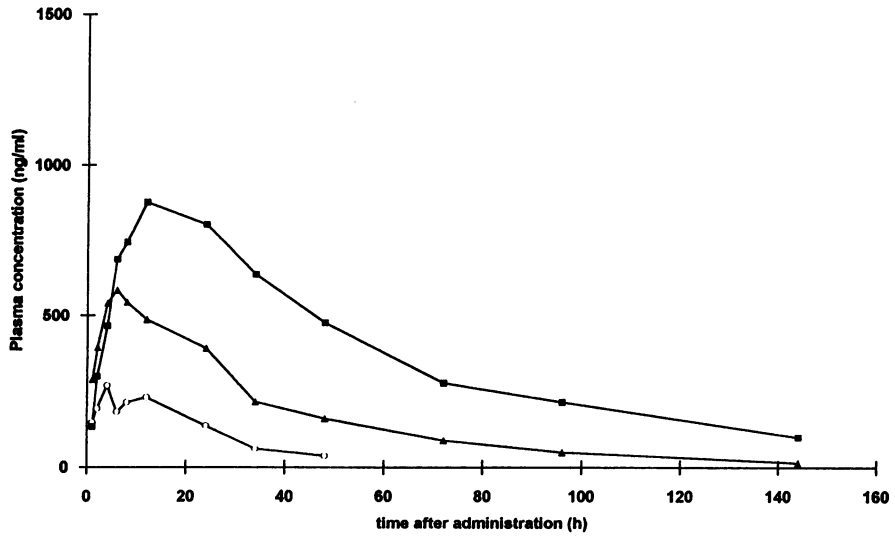

FIG. 3. Mean concentrations of conjugated sparfloxacin in the plasma of group I patients (▲), group II patients (■), and healthy subjects (○). The subjects were treated with a 400-mg oral dose of sparfloxacin.

C_{max}, ranging from 1,094 to 1,426 ng/ml, and AUC_{inf} increased in renal impairment patients. However, C_{max}, T_{max}, and AUC_{inf} of the three groups showed no statistically significant differences because of the high interindividual variability, especially of the AUC values, observed in patients. Mean $t_{1/2}$ in healthy subjects was 19.1 h. $t_{1/2}$ in renally impaired patients averaged 34.9 h (group I) and 38.5 h (group II), which represents significant increases of 83 and 102%, respectively, above the values seen for healthy subjects. The CL_P decreased in groups I and II, and this difference between group II and the healthy subjects was statistically significant. There was no significant relationship between CL_P and CL_{CR} of patients, which may be due to the narrow range of differences in CL_R. A slight decrease of nonrenal clearance for renal impairment patients (13 and 30% for groups I and II, respectively) compared with that for the healthy subjects was observed. However, this decrease was not statistically significant and was without relationship to CL_{CR}. This means that the nonrenal process for sparfloxacin elimination (mainly metabolism via glucuronidation, biliary excretion, and possibly intestinal secretion) was moderately modified in renally impaired patients. The mean level of urinary excretion in renal failure patients decreased significantly from 9.70% of the dose for healthy subjects to 4.04 and 3.19% of the dose for groups I and II, respectively. As shown in Table 2, large decreases in CL_R (67 and 77%, respectively) in groups I and II, compared with that for the healthy subjects, were observed. Sparfloxacin CL_R was correlated with CL_{CR} of groups I and II as shown in Fig. 2.

Mean levels of conjugated sparfloxacin in plasma are illustrated in Fig. 3. The mean pharmacokinetic data are compiled in Table 3. Mean C_{max} (678 ± 180 and 981 ± 590 ng/ml) represented approximately 47.5 and 74.5% of parent sparfloxacin peak levels for group I and group II patients, respectively. An important accumulation of the metabolite in plasma was observed, with levels higher than those of the unchanged drug in four of seven group II patients. C_{max} increased considerably in group II patients, as did AUC_{inf}, which increased approximately 3.7-fold in group I patients and 9.7-fold in group II patients above values determined for the healthy subjects. The statistical analysis showed a significant difference between the three groups of subjects, but no evident relationship between AUC and CL_{CR} could be determined. $t_{1/2}$ increased significantly (55 and 129%) in the two renal impairment patient groups. The urinary excretion of conjugated sparfloxacin decreased significantly in renal failure patients, ranging from 21.62% in healthy subjects to 9.78 and 8.39% in groups I and II, respectively. A significant decrease in CL_R was also observed: it represented less than 10 and 4% of CL_R observed for healthy subjects. A correlation between the CL_R and CL_{CR} of the patients was established (Fig. 4).

DISCUSSION

In healthy subjects, sparfloxacin was eliminated mainly via nonrenal processes, since CL_R of the unchanged drug accounted for only 9.6% of CL_P. CL_R of the glucuronide was

TABLE 3. Mean pharmacokinetic parameters of conjugated sparfloxacin following oral administration of 400 mg of sparfloxacin[a]

Group	C_{max} (ng/ml)	T_{max} (h) median[b]	AUC_t (ng · h/ml)	AUC_{inf} (ng · h/ml)	$t_{1/2}$ (h)	Urinary excretion (% of dose)	CL_R (ml/min)
I (n = 7)	678 ± 180	6 (2–24)	22,395 ± 7,111	25,482* ± 7,165	23.7* ± 3.9	9.78[a] ± 4.29	31.5[a] ± 18.1
II (n = 7)	981 ± 590	12 (4–24)	52,384 ± 36,909	64,943[a,b]** ± 36,957	35.0[a,b]** ± 8.6	8.39[a] ± 4.73	14.0[a] ± 7.2
III (n = 6)	353 ± 128	5 (2–16)	NA	6,840 ± 4,284	15.3 ± 3.8	21.62 ± 3.79	327 ± 280

[a] Parameters given are means ± standard deviations. a, significantly different from healthy subjects ($P < 0.05$); b, significantly different from group I; *, n = 5; **, n = 6. NA, not available.

[b] Ranges are indicated in parentheses.

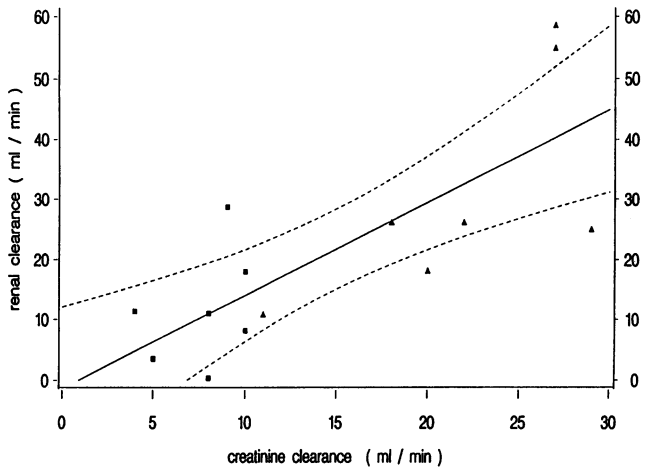

FIG. 4. Conjugated sparfloxacin CL_R versus measured CL_{CR} in group I patients (▲) and group II patients (■). The regression equation found is as follows: $CL_R = 0.0442\ CL_{CR} + 0.3757$; $r^2 = 0.68$, $r = 0.82$, $P > F = 0.0019$. The 95% confidence limit for the mean is indicated by the dashed lines.

15-fold that of the unchanged drug and exceeded the glomerular filtration rate for healthy subjects. Elimination of sparfloxacin was notably impaired in patients with chronic renal failure. That of glucuronide was markedly decreased, since levels of conjugated sparfloxacin in plasma were about 4 to 10 times higher than those achieved for healthy subjects. These results were not expected, since the renal excretion of parent and conjugated drugs represented only 31.3% of the dose in healthy volunteers. This difference from healthy subjects could only with difficulty be related to a difference in ages, since other kinetic studies of sparfloxacin in healthy elderly subjects after single or repeated dose administration did not evidence that the drug kinetics could change because of the age of the patient (11).

The fact that sparfloxacin and its glucuronide are cleared both by renal and nonrenal processes could explain the lack of an evident relationship between the levels in plasma and the degree of renal failure as evaluated by CL_{CR}.

The possible in vivo hydrolysis of conjugated sparfloxacin to the parent drug and the probable existence in humans of an enterohepatic cycle for sparfloxacin, involving possible hydrolysis of the glucuronide to the parent compound, as observed in rats (9), could explain why the elimination of unchanged drug has been found impaired in the patients studied here. The importance of this systemic cycling for drug glucuronides and the consequences for drug disposition have been pointed out recently (8). This systemic cycling could be responsible for a longer $t_{1/2}$ of free drug when drug glucuronide elimination is impaired. This impairment in glucuronide excretion is usually observed in cases of renal failure in which the glucuronides are cleared through the kidney. This is evident for sparfloxacin, as indicated by the relationship between sparfloxacin glucuronide CL_R and CL_{CR} of the patients. Moreover, the balance between intestinal absorption and intestinal secretion for sparfloxacin (14) may contribute to the cycle and could contribute to a complex phenomenon. This phenomenon could be responsible for the high intervariability of sparfloxacin levels in plasma, especially in patients with a physiological impairment such as renal failure. Taking into account the main results of this study, namely, no change in C_{max} and increase of drug $t_{1/2}$ in renally impaired patients, a possible therapeutic dosage regimen for sparfloxacin in cases of severe renal failure could be a 400-mg loading dose on day 1 followed by a 200-mg once-daily dose every 2 days.

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REFERENCES

1. **Barry, A. L., and P. C. Fuchs.** 1991. In vitro activities of sparfloxacin, tosufloxacin, ciprofloxacin, and fleroxacin. Antimicrob. Agents Chemother. **35:**955–960.
2. **Cockroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16:**31–34.
3. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, drugs and pharmaceutical sciences, p. 15. M. Dekker, New York.
4. **Iliadis, A.** 1987. APIS, version 2. User's guide Loginserm copyright. Institut National de la Santé et de la Recherche Médicale, MIIPS, Paris.
5. **Kanamaru, N., N. Nakashima, T. Uematsu, and Y. Takikuchi.** 1988. Pharmacokinetics and safety of a new quinolone, AT-4140 in healthy volunteers, abstr. 1490. Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, D.C.
6. **Kojima, T., M. Inoue, and S. Mitsuhashu.** 1989. In vitro activity of AT-4140 against clinical bacterial isolates. Antimicrob. Agents Chemother. **33:**1980–1988.
7. **Kojima, T., M. Inoue, and S. Mitsuhashu.** 1990. In vitro activity of AT-4140 against quinolone- and methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **34:**1123–1127.
8. **Kroemer, H. K., and U. Klotz.** 1992. Glucuronidation of drugs. A reevaluation of the pharmacological significance of the conjugates and modulating factors. Clin. Pharmacokinet. **23:**292–310.
9. **Matsunaga, Y., H. Miyazaki, Y. Oh-e, K. Nambu, H. Furukawa, K. Yoshida, and M. Hashimoto.** 1991. Disposition and metabolism of (^{14}C)sparfloxacin in the rat. Arzneim.-Forsch./Drug Res. **41:**747–759.
10. **Montay, G., R. Bruno, J. J. Thebault, J. C. Vergniol, D. Chassard, M. Ebmeier, and J. Gaillot.** 1990. Dose-dependent pharmacokinetic study of sparfloxacin (SPFX) in healthy young volunteers, abstr. 1248. Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, D.C.
11. **Montay, G., R. Bruno, J. C. Vergniol, J. Rey, A. Frydman, P. A. M. Peeters, I. Dhont, and J. H. G. Jonkman.** 1991. Pharmacokinetics of sparfloxacin after repeated administration in healthy elderly volunteers, abstr. 593. Program Abstr. 31st Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, D.C.
12. **Nakamura, S., N. Kurobe, T. Ohue, M. Hashimoto, and M. Shimizu.** 1990. Pharmacokinetics of a novel quinolone, AT-4140, in animals. Antimicrob. Agents Chemother. **34:**89–93.
13. **Nakamura, S., A. Minami, K. Nakata, N. Kurobe, K. Kouno, Y. Sakaguchi, S. Kashimoto, H. Yoshida, T. Kojima, T. Ohue, K. Fujimoto, M. Nakamura, M. Hashimoto, and M. Shimizu.** 1989. In vitro and in vivo antibacterial activities of AT-4140, a new broad-spectrum quinolone. Antimicrob. Agents Chemother. **33:** 1167–1173.
14. **Rubinstein, E., J. F. Huneau, A. M. Dumontier, and C. Carbon.** 1992. In vitro and ex vivo intestinal absorption and secretion of sparfloxacin, abstr. 1463. Program Abstr. 32nd Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, D.C.
15. **SAS Institute Inc.** SAS version 6.08. SAS Institute Inc., Cary, N.C.
16. **Segre, G.** 1986. Pharmacokinetics—compartmental representation, p. 53–68. *In* M. Rowland and G. Tucker (ed.), Pharmacokinetics. Theory and methodology. Pergamon Press, Inc., Elmsford, N.Y.