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Pharmacokinetics of a Novel Quinolone, AT-4140, in Animals

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The pharmacokinetics of 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (AT-4140) in experimental animals given a single oral dose of 5 mg/kg were studied. The mean peak levels of AT-4140 in plasma of mice, rats, dogs, and monkeys were 0.25, 0.50, 1.14, and 0.49 μg/ml, respectively, with mean elimination half-lives of 5.0, 3.8, 8.0, and 11.7 h, respectively. The oral bioavailability of AT-4140 calculated from the ratio of the areas under the concentration-time curve after oral and intravenous administration was 77% in dogs. The levels of AT-4140 in tissue in mice and rats were 1 to 11 times higher than the levels in plasma and 4 to 9 times higher than those of ciprofloxacin in mice. The mean 24-h biliary recovery of AT-4140 in rats was 5.6% of the dose and became 21.3% after β-glucuronidase treatment. The mean 48-h urinary recoveries of AT-4140 in mice, rats, dogs, and monkeys were 6.7, 12.9, 8.6, and 12.7%, respectively, of the dose and were 7.8, 16.3, 8.9, and 18.9%, respectively, after β-glucuronidase treatment. The pharmacokinetics of AT-4140 may be characterized by its good tissue penetration and its long half-life in plasma and tissues.

AT-4140 is a new quinolone derivative with broad and potent antibacterial activity against gram-positive and gram-negative organisms, glucose nonfermenters, anaerobes, *Mycoplasma* spp., *Chlamydia* spp., and *Mycobacterium* spp. (10). Its in vivo activity was generally superior to those of ciprofloxacin, ofloxacin, enoxacin, and norfloxacin in experimental infections in mice (10). This paper describes the pharmacokinetic properties of AT-4140 in experimental animals.

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MATERIALS AND METHODS

Drugs. AT-4140 (J. Matsumoto, T. Miyamoto, H. Egawa, and S. Nakamura, Chem. Abstr. **107**:236733v, 1987) and ciprofloxacin (4) were synthesized in our laboratory as reported previously. Doses and concentrations of the drugs are expressed in terms of the free bases.

Animals. The animals used were male Std-ddY mice weighing 22 to 38 g, male Wistar rats weighing 190 to 270 g, male beagle dogs weighing 11 to 13 kg, and male cynomolgus monkeys weighing 3.7 to 5.4 kg.

Drug administration. For oral administration, AT-4140 was suspended in 0.2% carboxymethylcellulose sodium solution (for mice and rats) or 0.5% gum tragacanth solution (for monkeys) and ciprofloxacin was dissolved in deionized water to avoid its aggregation in 0.2% carboxymethylcellulose sodium solution (for mice). Both the drugs were packed in gelatin capsules for oral administration to dogs. For intravenous administration, the drugs were dissolved in physiological saline with an appropriate amount of NaOH if necessary. The drugs were administered once at a dose of 5 mg/kg to animals that had fasted overnight, unless otherwise specified.

Preparation of assay samples. Blood was withdrawn by cardiac puncture from mice and rats under ether anesthesia at 0.25, 0.5, 1, 2, 4, 6, and 8 h postadministration and by venipuncture from dogs and monkeys at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after oral administration and 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after intravenous administration. Blood samples were centrifuged to separate the plasma. Organs and tissues were harvested from exsanguinated mice 0.5, 1, 2, 4, 6, and 8 h postadministration and from exsanguinated rats 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h postadministration. Spinal fluid was taken from the same rats by puncturing the atlanto-occipital membrane by the method of Yaksh and Rudy (17) before exsanguination. Tissue extracts were prepared as described previously (9). Bile was collected from rats through a polyethylene catheter introduced into the common bile duct by surgery and pooled for 0 to 3, 3 to 6, and 6 to 24 h. Urine was collected from a group of five mice housed in a metabolism cage and from rats, dogs, and monkeys individually housed in metabolism cages. Urine was pooled for 0 to 6, 6 to 24, and 24 to 48 h for mice and rats and for 0 to 24 and 24 to 48 h for dogs and monkeys. Bile and urine were sometimes treated with 1,000 U of β-glucuronidase B-10 (Sigma Chemical Co., St. Louis, Mo.) per ml as reported previously (2) or heated at 100°C for 2 h after fivefold dilution with 0.2 N NaOH to hydrolyze conjugates. All samples were stored at −20°C until assayed.

Bioassay. The drug concentrations were determined by the agar well diffusion method with *Escherichia coli* Kp. The organism was grown in nutrient broth (Eiken Co., Ltd., Tokyo, Japan) at 37°C overnight. Molten assay agar consisting of 12.5 g of heart infusion broth (Difco Laboratories, Detroit, Mich.) and 15.8 g of agar (Difco) per liter, kept at 44°C, was inoculated with the organism culture in 1%, and 12-ml portions were poured into plates (diameter, 90 mm; Terumo, Tokyo, Japan) and solidified. The agar plates were stored at 5°C until use. Four wells (diameter, 8 mm) per plate were made with a hole puncher (AHP-104; Tokyo M.I. Shokai, Tokyo, Japan) and filled with 60 μl of sample solutions diluted with 1/15 M phosphate buffer (pH 7). Three wells were used for each sample, and five wells were used for a standard solution. Standard solutions of AT-4140 and ciprofloxacin were made in 1/15 M phosphate buffer (pH 7) at concentrations ranging from 0.025 to 0.2 μg/ml. When plasma samples were assayed without being diluted at least

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threefold, the standard solutions were made in the presence of plasma to the same content as the samples. After incubation at 37°C for 18 h, the diameters of the inhibitory zones were measured and converted to concentrations by using video analyzing equipment (502A; DAC Engineering Co., Ltd., Kyoto, Japan) connected to a personal computer (PC-9801vm; NEC Corp., Tokyo, Japan). Calibration lines were made by using a linear least-squares regression with the computer; these lines were linear over the standard curve range for both the drugs. The coefficients of inter- and intraday variation at 0.04 and 0.12 μg/ml were <5% and <15%, respectively, for both the drugs, whose sensitivities were both about 0.01 μg/ml.

Pharmacokinetic analysis. Plasma concentration-time data were fitted to a one- or two-compartment open model according to the curves of plotted data, and constants for multiexponential equations (3, 4, 7) were computed by an unweighted nonlinear least-squares program, MULTI (18). The pharmacokinetic parameters maximal concentration (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$) in the elimination phase, area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$), apparent volume of distribution (V_{area}), and clearance (CL) were calculated from the constants of the equations by standard methods as described previously (3, 12). The oral bioavailability was calculated from the ratio of the $AUC_{0-\infty}$ values after oral and intravenous administration.

Tissue concentration-versus-time data in mice were insufficient to be applied to MULTI, so parameters were estimated as follows: C_{max}, maximal concentration observed; $t_{1/2}$, elimination half-life calculated by linear least-squares regression; and $AUC_{0-\infty}$, area under the concentration-time curve calculated by the trapezoidal rule and extrapolated to infinity by dividing the last observed concentration by the elimination rate constant.

Statistics. Differences between AT-4140 and ciprofloxacin bioavailability in dogs and tissue penetration in mice were analyzed by Student's *t* test and the Wilcoxon nonparametric signed-rank test, respectively.

RESULTS

Levels in plasma. The AT-4140 levels in plasma and its pharmacokinetic parameters in animals given a single oral dose of 5 mg/kg are shown in Fig. 1 and Table 1. The C_{max}s of AT-4140 were 0.25, 0.50 ± 0.07 (mean ± standard deviation), 0.49 ± 0.27, and 1.14 ± 0.12 μg/ml with $t_{1/2}$s of 5.0, 3.8 ± 1.6, 11.7 ± 4.9, and 8.0 ± 1.1 h in mice, rats, monkeys, and dogs, respectively. There was a tendency for the C_{max}s and $t_{1/2}$s to be generally higher and longer in larger animals than in smaller ones. Therefore, the $AUC_{0-\infty}$s decreased in the order dogs > monkeys > rats > mice. For estimating the oral bioavailability of AT-4140 and ciprofloxacin, the levels in plasma of dogs after oral and intravenous administration were compared (Fig. 2). The plasma concentration-time curves of AT-4140 given orally and intravenously were almost the same 4 h postadministration, and the bioavailability of AT-4140 was calculated to be 77%. On the other hand, the curves for ciprofloxacin given orally and intravenously were different throughout the measuring time points, and the bioavailability was calculated to be 42%. The bioavailability of AT-4140 was significantly higher than that of ciprofloxacin ($P < 0.05$). The V_{area}s of AT-4140 and ciprofloxacin were 3.28 ± 0.30 and 1.70 ± 0.19 liters/kg, respectively, and their CLs were 3.65 ± 0.67 and 7.86 ± 0.14 ml/min per kg, respectively, in dogs after intravenous administration (Table 1).

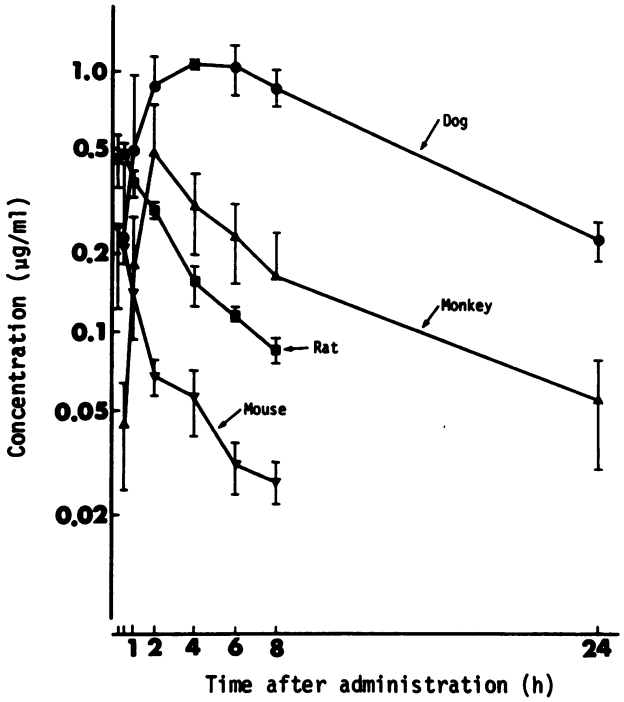

FIG. 1. Levels of AT-4140 in plasma in mice (▼, $n = 5$), rats (■, $n = 5$), dogs (●, $n = 3$), and monkeys (▲, $n = 4$) given a single oral dose of 5 mg/kg. Each point represents mean ± standard deviation (SD).

Levels in tissue. The levels of AT-4140 in tissues of nonfasted rats receiving a single oral dose of 5 mg/kg were determined (Fig. 3). Most levels reached a peak at 0.5 h postadministration and then fell with almost the same kinetics as the levels in plasma. The peak concentrations of AT-4140 in plasma and in muscle, heart, lung, spleen, prostate, liver, and kidney tissue were 0.24 ± 0.09, 0.28 ± 0.07, 0.78 ± 0.12, 0.79 ± 0.28, 0.73 ± 0.12, 0.68, 1.86 ± 0.39, and 2.53 ± 0.37 μg/ml or μg/g, respectively. The levels in tissue were 1 to 11 times higher than the level in plasma. In contrast, the peak level in spinal fluid was 0.043 μg/ml, lower than that in plasma, and AT-4140 was not detectable (<0.09 μg/g) in brain tissue. All the levels in tissue had fallen below the assay limit (<0.04 μg/g) by 24 h postadministration. The levels of AT-4140 in tissue were compared with those of ciprofloxacin in mice given a single oral dose of 5 mg/kg. The C_{max}s of AT-4140 in plasma and heart, lung, kidney, and muscle tissue were 0.19 ± 0.03, 0.37 ± 0.09, 0.72 ± 0.10, 1.31 ± 0.26, and 0.42 ± 0.12 μg/ml or μg/g, respectively, with $t_{1/2}$s of 2.7 to 3.3 h, and those of ciprofloxacin were 0.07 ± 0.02, 0.10 ± 0.02, 0.08 ± 0.02, 0.23 ± 0.06, and 0.07 ± 0.01 μg/ml or μg/g, with $t_{1/2}$s of 0.9 to 1.8 h (Fig. 4; Table 2). The C_{max}s of AT-4140 were 4 to 9 times higher than those of ciprofloxacin, and the $t_{1/2}$s of AT-4140 were 2 to 3 times longer than those of ciprofloxacin. Consequently, the $AUC_{0-\infty}$s of AT-4140 in plasma and heart, lung, kidney, and muscle tissue were 0.83, 1.49, 3.09, 5.41, and 2.00 μg · h/ml or μg · h/g, respectively, which were 5 to 14 times greater than those of ciprofloxacin. The ratios of $AUC_{tissue}/AUC_{plasma}$ of AT-4140 as an index of tissue penetration were significantly higher than those of ciprofloxacin ($P < 0.05$).

Excretion. The biliary excretion of AT-4140 in rats given a single oral dose of 5 mg/kg is shown in Table 3. AT-4140

TABLE 1. Pharmacokinetic parameters of AT-4140 and ciprofloxacin on the levels in plasma in animals given a single oral dose of 5 mg/kg[a]

Drug and route	Animal (n)	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/ml)	V_{area} (liters/kg)	CL (ml/min per kg)
AT-4140 (oral)	Mouse (n = 5)[b]	0.25	0.3	5.0	0.74		
	Rat (n = 5)	0.50 ± 0.07	0.4 ± 0.2	3.8 ± 1.6	2.05 ± 0.26		
	Monkey (n = 4)	0.49 ± 0.27	2.0 ± 0.5	11.7 ± 4.9	4.61 ± 1.62		
	Dog (n = 3)	1.14 ± 0.12	3.9 ± 2.0	8.0 ± 1.1	17.74 ± 1.88		
AT-4140 (intravenous)	Dog (n = 3)			10.5 ± 1.3	23.35 ± 4.6	3.28 ± 0.30	3.65 ± 0.67
Ciprofloxacin (oral)	Dog (n = 3)	0.70 ± 0.37	1.7 ± 0.8	3.3 ± 1.1	4.77 ± 2.70		
Ciprofloxacin (intravenous)	Dog (n = 3)			2.6 ± 0.7	10.81 ± 1.74	1.70 ± 0.19	7.86 ± 0.14

[a] Values are means ± standard deviations.
[b] Values are calculated from the data of mean concentrations.

levels were 13.8 ± 3.7, 8.5 ± 4.4, and 3.7 ± 1.3 μg/ml in bile pooled for 0 to 3 h, 3 to 6 h, and 6 to 24 h, respectively, and the 24-h biliary recovery of AT-4140 was 5.6 ± 1.1% of the dose. The levels in bile and recoveries increased four- or sixfold after β-glucuronidase treatment or heating with NaOH.

Table 4 shows the urinary excretion of AT-4140 in mice, rats, dogs, and monkeys given a single oral dose of 5 mg/kg. The peak levels of AT-4140 in urine were 5.1 μg/ml in mice (0 to 6 h), 22.2 ± 8.4 μg/ml in rats (0 to 6 h), 14.5 ± 0.7 μg/ml in dogs (0 to 24 h), and 10.8 ± 3.1 μg/ml in monkeys (0 to 24 h), and the 48-h urinary recoveries were 6.7, 12.9 ± 4.0, 8.6 ± 0.1, and 12.7 ± 1.2%, respectively. β-Glucuronidase treatment resulted in about 20 to 50% increases in urinary recoveries in rats and monkeys, but no significant change in mice and dogs. The active substance in urine was only unchanged AT-4140 in all animals when checked by bioautography of the thin-layer chromatogram (data not shown).

DISCUSSION

When AT-4140 was administered to mice, rats, dogs, and monkeys at an oral dose of 5 mg/kg, its C_{max}s were 0.25, 0.50, 1.14, and 0.49 μg/ml and its $t_{1/2}$s were 5.0, 3.8, 8.0, and 11.7 h, respectively. These levels seem to be above its MICs for most pathogenic organisms, which are usually inhibited by AT-4140 concentrations below 0.1 μg/ml (10). It has been reported that the C_{max}s of enoxacin and norfloxacin in dogs given an oral dose of 25 mg/kg are 5.13 and 0.79 μg/ml, respectively, and that the elimination half-lives of enoxacin and norfloxacin are 5.8 and 6.1 h, respectively (9). Therefore, the level of AT-4140 in plasma in dogs is higher than that of norfloxacin, and the $t_{1/2}$ of AT-4140 is longer than that

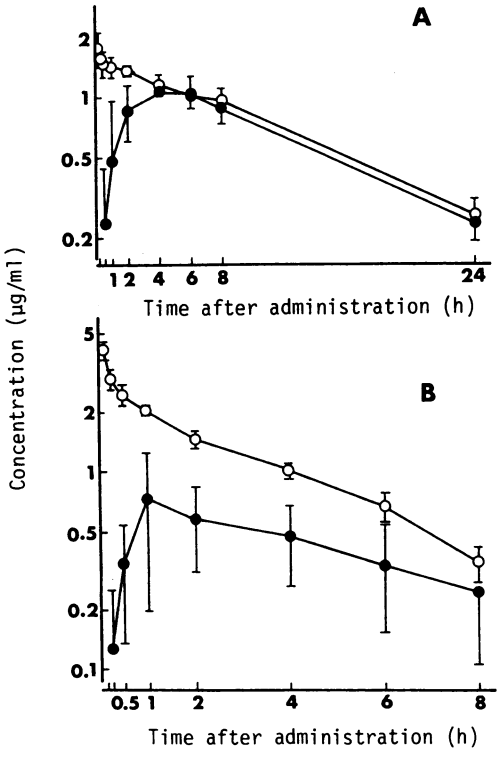

FIG. 2. Levels of AT-4140 (A) (n = 3) and ciprofloxacin (B) (n = 3) in plasma in dogs given a single intravenous (○) or oral (●) dose of 5 mg/kg. Each point represents mean ± SD.

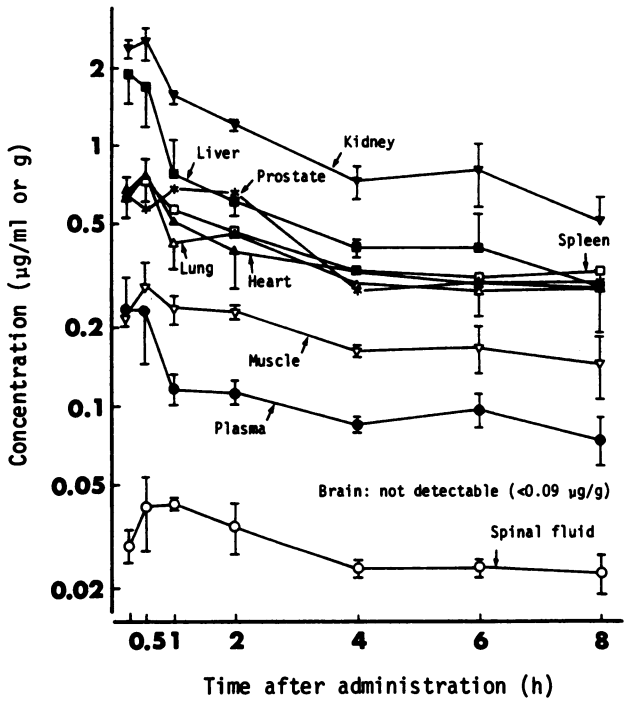

FIG. 3. Concentrations of AT-4140 in kidney (▼), liver (■), prostate (*), spleen (□), heart (▲), lung (△), and muscle (▽) tissue, plasma (●), and spinal fluid (○) of nonfasted rats given a single oral dose of 5 mg/kg. Each point represents mean ± SD (n = 3).

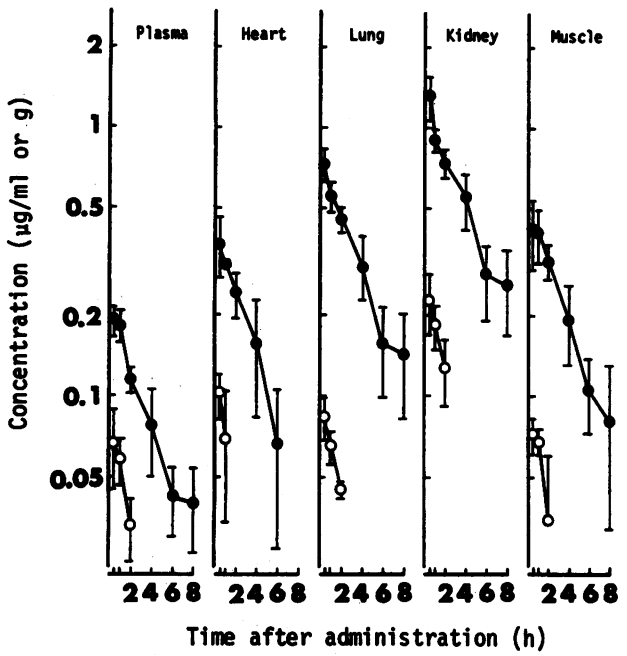

FIG. 4. Concentrations of AT-4140 (●) and ciprofloxacin (○) in plasma, heart, lung, kidney, and muscle tissue of mice given a single oral dose of 5 mg/kg. Each point represents mean ± SD (n = 5).

TABLE 2. Pharmacokinetic parameters of AT-4140 and ciprofloxacin on the levels in tissue in mice given a single oral dose of 5 mg/kg

Plasma or tissue	Drug	C_{max}[a] (μg/ml or g)	$t_{1/2}$[b] (h)	$AUC_{0-\infty}$[b] (μg · h/ml or μg · h/g)	$AUC_{tissue}/AUC_{plasma}$
Plasma	AT-4140	0.19 ± 0.03	3.1	0.83	1.0
	Ciprofloxacin	0.07 ± 0.02	1.4	0.16	1.0
Heart	AT-4140	0.37 ± 0.09	2.7	1.49	1.8
	Ciprofloxacin	0.10 ± 0.02	0.9	0.16	1.0
Lung	AT-4140	0.72 ± 0.10	3.1	3.09	3.7
	Ciprofloxacin	0.08 ± 0.02	1.7	0.22	1.4
Kidney	AT-4140	1.31 ± 0.26	3.3	5.41	6.5
	Ciprofloxacin	0.23 ± 0.06	1.8	0.65	4.1
Muscle	AT-4140	0.42 ± 0.12	3.0	2.00	2.4
	Ciprofloxacin	0.07 ± 0.01	1.0	0.16	1.0

[a] Values are means ± standard deviations (n = 5).
[b] Values are calculated from the data of mean concentrations.

of enoxacin and norfloxacin, although the doses used are different. The $t_{1/2}$s of AT-4140 in dogs were comparable to those of fleroxacin, a quinolone with a long $t_{1/2}$ (7). The reason why the elimination of AT-4140 is slow is not clear at present. The serum protein binding of AT-4140 was about 44% (H. Miyazaki, personal communication), which would not account for its slow elimination, but its enterohepatic circulation (Y. Sekine, Y. Matsunaga, H. Miyazaki, T. Yamaguchi, Y. Mizuki, T. Itoh, N. Kurobe, S. Nakamura, M. Hashimoto, and M. Shimizu, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1489, 1988) may partly explain it. Similar enterohepatic circulation has been reported with lomefloxacin (13). The oral bioavailabilities of AT-4140 and ciprofloxacin in dogs were 77 and 42%, respectively, and the former was significantly better than the latter in oral absorption.

The levels of AT-4140 in tissue were generally higher than its levels in plasma in rats and mice. The levels in heart, lung, spleen, muscle, and prostate tissue were 2 to 3 times higher and the levels in liver and kidney were 7 to 11 times higher than the level in plasma in rats. The levels of enoxacin and norfloxacin in tissue were also higher than the levels in plasma in rats (9). However, the penetration of AT-4140 into tissues, expressed as ratios of the levels in tissues to the level in plasma, was generally better than that of enoxacin and norfloxacin in rats (9) and better than that of ciprofloxacin in mice (Table 2). Such good tissue penetration of AT-4140 was consistent with its relatively large V_{area}s. Irrespective of its good tissue penetration, its levels in brain tissue and spinal fluid were low in rats, indicating its poor penetration into the central nervous system. The elimination kinetics of AT-4140 in tissues were almost the same as those in plasma, demonstrating that high levels in tissue might be maintained for longer periods with AT-4140 than with enoxacin, norfloxacin, or ciprofloxacin.

Absorbed AT-4140 was excreted into bile and urine. About 6% of the dose was excreted as an active form in rat bile for 24 h, and the excretion rate increased to 21 or 31% after β-glucuronidase treatment or heating with NaOH. AT-4140 was excreted into urine of mice, rats, dogs, and monkeys at about 7, 13, 9, and 13% of the dose, respectively, for 48 h as unchanged AT-4140 and at about 8, 16, 9, and 19% of the dose, respectively, when assayed after the β-glucuronidase treatment. The results indicate that AT-4140 is partly metabolized into a glucuronide, at least in rats and monkeys. The total recovery of AT-4140 from bile and urine of rats was only about 47%. Since a study with [^{14}C]AT-4140 has revealed that about 20 and 80% of the intravenous dose is excreted into urine and feces in rats (Sekine et al., 28th ICAAC), most of the remainder of the dose in this study would be excreted in feces.

TABLE 3. Biliary excretion of AT-4140 in rats given a single oral dose of 5 mg/kg

Excretion period (h)	Concn (μg/ml)[a]			Recovery (%)[a]		
	AT-4140 only	After β-glucuronidase treatment	After heating at 100°C with NaOH	AT-4140 only	After β-glucuronidase treatment	After heating at 100°C with NaOH
0–3	13.8 ± 3.7	60.7 ± 21.7	84.7 ± 13.8	2.5 ± 0.8	11.4 ± 4.8	15.6 ± 3.1
3–6	8.5 ± 4.4	29.8 ± 9.2	48.4 ± 16.6	0.9 ± 0.3	3.4 ± 0.7	5.5 ± 1.3
6–24	3.7 ± 1.3	11.2 ± 2.3	16.0 ± 2.9	2.1 ± 0.4	6.6 ± 1.2	9.5 ± 2.0
Total (0–24)				5.6 ± 1.1	21.3 ± 4.6	30.5 ± 3.3

[a] Values are means ± standard deviations (n = 5).

TABLE 4. Urinary excretion of AT-4140 in animals given a single oral dose of 5 mg/kg

Excretion period (h)	Concn (μg/ml)[a] in:				Recovery (%)[a] in:			
	Mice[b] (n = 5)	Rats (n = 5)	Dogs (n = 3)	Monkeys (n = 4)	Mice[b] (n = 5)	Rats (n = 5)	Dogs (n = 3)	Monkeys (n = 4)
0–6	5.1 (4.8)	22.2 ± 8.4 (29.1 ± 8.8)			2.0 (1.9)	8.6 ± 2.9 (11.1 ± 1.9)		
			14.5 ± 0.7 (15.2 ± 0.8)	10.8 ± 3.1 (16.8 ± 8.6)			6.1 ± 0.7 (6.4 ± 1.0)	10.1 ± 0.6 (15.2 ± 4.0)
6–24	3.6 (4.6)	8.0 ± 2.7 (9.3 ± 1.8)			3.7 (4.7)	(4.5 ± 0.6)		
24–48	1.0 (1.1)	0.8 ± 0.3 (1.0 ± 0.4)	3.8 ± 1.7 (3.9 ± 2.3)	2.8 ± 1.6 (4.3 ± 3.0)	1.0 (1.1)	0.4 ± 0.1 (0.5 ± 0.1)	2.5 ± 0.7 (2.5 ± 1.1)	2.7 ± 0.8 (3.8 ± 1.1)
Total (0–48)					6.7 (7.8)	12.9 ± 4.0 (16.3 ± 1.4)	8.6 ± 0.1 (8.9 ± 0.3)	12.7 ± 1.2 (18.9 ± 5.0)

[a] Values are means ± standard deviations. Values in parentheses indicate the data after treatment with β-glucuronidase.
[b] Urine of five mice in a cage was pooled.

From these results, the pharmacokinetic properties of AT-4140 may be characterized by its good oral absorption, its sufficient levels in plasma, its good tissue penetration, and its long duration in plasma and tissues. In the experimental infection models in mice, AT-4140 was effective against systemic, pulmonary, dermal, and urinary tract infections due to a variety of organisms, and its efficacies were generally better than those of ciprofloxacin, ofloxacin, enoxacin, and norfloxacin (10). An interesting finding was that AT-4140 was more effective than ciprofloxacin even in the infections with organisms which were less susceptible to AT-4140 than to ciprofloxacin in vitro. The pharmacokinetic characteristics of AT-4140 may account for its good in vivo effect.

The phase I study (M. Kanamaru, M. Nakashima, T. Uematsu, and Y. Takikuchi, 28th ICAAC, abstr. no. 1490, 1988) disclosed that the C_{max}s of AT-4140 were 0.44, 0.65, and 1.39 μg/ml at single oral doses of 100, 200, and 400 mg per person (1.5, 3.1, and 6.3 mg/kg), respectively, with $t_{1/2}$s of 16.8, 16.3, and 16.0 h, and that about 10% of the dose (200 mg per person) was excreted into urine for 72 h as unchanged AT-4140, 25% was excreted into urine as an AT-4140 glucuronide, and 56% was excreted into feces as unchanged AT-4140. Therefore, humans are similar to rats and monkeys in terms of the metabolism of AT-4140. The C_{max}s of AT-4140 in humans seem to be comparable to those in dogs, although the $t_{1/2}$s in humans are twice as long as those in dogs. The $t_{1/2}$ of AT-4140 in humans, which is longer than those of ciprofloxacin, ofloxacin, enoxacin, norfloxacin, fleroxacin, tosufloxacin (T-3262), and pefloxacin (1, 5, 6, 11, 14, 15, 16, 19), suggests that once-a-day treatment is a possibility.

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LITERATURE CITED

1. **Barre, J., G. Houin, and J. P. Tillement.** 1984. Dose-dependent pharmacokinetic study of pefloxacin, a new antibacterial agent, in humans. J. Pharm. Sci. **73**:1379–1382.
2. **DiCarlo, F. J., M. C. Crew, and R. C. Greenough.** 1968. Biotransformation of the methylenedioxy moiety of oxolinic acid in man. Arch. Biochem. Biophys. **127**:503–511.
3. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **293**:702–705, 964–970.
4. **Grohe, K., and H. Heitzer.** 1987. Synthese von 4-Chinolone-3-Carbonsäuren. Liebigs Ann. Chem. **1987**:29–37.
5. **Höffken, G., H. Lode, C. Prinzing, K. Borner, and P. Koeppe.** 1985. Pharmacokinetics of ciprofloxacin after oral and parenteral administration. Antimicrob. Agents Chemother. **27**:375–379.
6. **Kawai, M., M. Nakashima, and N. Maekawa.** 1984. Phase I study of AT-2266. Chemotherapy **32**(Suppl. 3):334–358.
7. **Kusajima, H., N. Ishikawa, M. Machida, H. Uchida, and T. Irikura.** 1986. Pharmacokinetics of a new quinolone, AM-833, in mice, rats, rabbits, dogs, and monkeys. Antimicrob. Agents Chemother. **30**:304–309.
8. **LeBel, M., F. Vallée, and M. G. Bergeron.** 1986. Tissue penetration of ciprofloxacin after single and multiple doses. Antimicrob. Agents Chemother. **29**:501–505.
9. **Nakamura, S., N. Kurobe, S. Kashimoto, T. Ohue, Y. Takase, and M. Shimizu.** 1983. Pharmacokinetics of AT-2266 administered orally to mice, rats, dogs, and monkeys. Antimicrob. Agents Chemother. **24**:54–60.
10. **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 activity of AT-4140, a new broad-spectrum quinolone. Antimicrob. Agents Chemother. **33**:1167–1173.
11. **Ogawa, N., H. Uchida, S. Murayama, K. Hirai, Y. Oomori, Y. Abe, and T. Irikura.** 1981. Phase I study on AM-715. Chemotherapy (Tokyo) **29**(Suppl. 4):136–145.
12. **Park, G. B., J. Saneski, T. Weng, and J. Edelson.** 1982. Pharmacokinetics of rosoxacin in human volunteers. J. Pharm. Sci. **71**:461–462.
13. **Saito, A., O. Nagata, Y. Takahara, E. Okezaki, T. Yamada, and Y. Ito.** 1988. Enterohepatic circulation of NY-198, a new difluorinated quinolone, in rats. Antimicrob. Agents Chemother. **32**:156–157.
14. **Tartaglione, T. A., A. C. Raffalovich, W. J. Poynor, A. Espinel-Ingroff, and T. M. Kerkering.** 1986. Pharmacokinetics and tolerance of ciprofloxacin after sequential increasing oral doses. Antimicrob. Agents Chemother. **29**:62–66.
15. **Wise, R., B. Kirkpatrick, J. Ashby, and D. J. Griggs.** 1987. Pharmacokinetics and tissue penetration of Ro 23-6240, a new trifluoroquinolone. Antimicrob. Agents Chemother. **31**:161–163.
16. **Wise, R., R. Lockley, J. Dent, and M. Webberly.** 1984. Pharmacokinetics and tissue penetration of enoxacin. Antimicrob. Agents Chemother. **26**:17–19.
17. **Yaksh, T. L., and T. A. Rudy.** 1976. Chronic catheterization of the spinal subarachnoid space. Physiol. Behav. **17**:1031–1036.
18. **Yamaoka, K., Y. Tanigawara, T. Nakagawa, and T. Uno.** 1981. A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobio-Dyn. **4**:879–885.
19. **Yamasaku, F., and Y. Suzuki.** 1988. A comparative study of the pharmacokinetic of ofloxacin, ciprofloxacin, NY-198 and T-3262 in the same volunteers. Chemotherapy (Tokyo) **36**(Suppl. 9):195–200.