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Pharmacokinetics of a New Quinolone, AM-833, in Mice, Rats, Rabbits, Dogs, and Monkeys

HISAO KUSAJIMA, NORIHISA ISHIKAWA, MASAAKI MACHIDA, HIROSHI UCHIDA,* AND TSUTOMU IRIKURA

Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan

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The pharmacokinetics of AM-833 [6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid] were studied in mice, rats, rabbits, dogs, and monkeys by reversed-phase high-performance liquid chromatography. AM-833 was rapidly and completely absorbed from the digestive tracts of mice, rats, and dogs. About half of AM-833 bound to rat and dog serum proteins. Drug levels in lung, spleen, liver, and kidney tissues of rats and dogs were greater than the respective levels in serum but lower in brain tissue. Drug levels in tissues declined with the decrease in levels in serum. AM-833 penetrated rapidly and well into inflammatory exudate of rats. Elimination half-lives in serum were species dependent, ranging from 1.57 h in rabbits to 9.42 h in dogs. Profiles of drug levels in serum were dose related over a single dose range from 2 to 40 mg/kg and not modified significantly during multiple dosing in dogs. Unchanged AM-833 was excreted in urine and bile in both rats and dogs. The metabolism of AM-833 was suggested by evidence that 24-h total recovery of unchanged AM-833 in urine and bile accounted for about half of the intravenous dose in rats.

6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (AM-833) is a new pyridonecarboxylic acid derivative (Fig. 1) with potent and broad in vitro antibacterial activity against gram-positive and gram-negative bacteria (1). The compound also exhibited significant activity against various experimental infections (1). This paper describes the absorption, distribution, and excretion of AM-833 in various experimental animals.

(This work was presented in part at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nev., 24 to 26 October 1983 [K. Takagi, M. Hosaka, H. Kusajima, Y. Oomori, K. Hirai, H. Uchida, and T. Irikura, Program Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 659, 1983].)

MATERIALS AND METHODS

Chemicals. AM-833 (lot no. 830530) and an internal standard (1-ethyl-6-fluoro-1,4-dihydro-7-imidazol-1-yl-4-oxo-3-quinolinecarboxylic acid) for analysis were synthesized in our laboratories. All other reagents were of analytical grade.

Animals. Male ICR mice (body weight, about 30 g), male Wistar rats (250 to 450 g), male Japanese White rabbits (3.1 to 3.5 kg), male and female beagle dogs (8.5 to 13.0 kg), male mongrel dogs (8.5 and 11.0 kg), and male cynomolgus monkeys (5.0 to 5.7 kg) were treated. Unless otherwise stated, male beagle dogs were used.

Drug administration. AM-833 was administered to fasting animals except when repeatedly given to dogs. A suspension for oral administration was prepared by homogenizing the powder in 0.3 to 0.5% carboxymethyl cellulose sodium aqueous solution. An aqueous solution for intravenous and oral administration was prepared by dissolving AM-833 in 0.1 N sodium hydroxide and then adjusting the pH to 9 to 10 with 2 N hydrochloric acid in which osmolarity was maintained at physiological pressure by addition of sodium chloride. Single oral doses were given to 30 mice (10 or 50 mg/kg) and 4 rats (10 mg/kg) as suspensions and to 6 dogs (2, 10, or 40 mg/kg) as hard gelatin capsules. Additional single oral doses were given to four rats (10 mg/kg) and six dogs (2 or 10 mg/kg) as an aqueous solution. Repeated oral doses were given to three dogs twice daily (0, 8, 24, 32, 48, 56, 72, 80, and 96 h after the first dose) for 5 days at a dose of 2 mg/kg as capsules. Bolus intravenous doses were given to 40 mice (10 or 50 mg/kg by tail vein), 4 rabbits (10 mg/kg by ear vein), 6 dogs (2 or 10 mg/kg by foreleg vein), and 3 monkeys (10 mg/kg by leg vein) by direct injection and to 4 rats (10 mg/kg) through a polyethylene catheter inserted into the femoral vein. For determination of levels in tissues, AM-833 was given to five rats as a bolus injection (3.90 mg/kg) and then infused at a rate of 1.05 mg/kg per h for 2 h, and AM-833 was given to three female beagle dogs as a bolus injection (6.84 mg/kg) and then infused at a rate of 0.50 mg/kg per h for 3.5 h through a polyethylene catheter introduced into the femoral and foreleg veins, respectively. In an experiment on urinary and biliary excretion in dogs, the aqueous solution (10 mg/kg) was intravenously given to two male mongrel dogs via a polyethylene catheter inserted into the foreleg vein. Ringer solution containing 0.8% (wt/vol) glucose was intravenously given dropwise at a rate of 40 ml/h during collection of urine and bile samples. In four rats AM-833 (10 mg/kg) was intravenously injected through a polyethylene catheter inserted into the femoral vein for collection of urine and bile. The granuloma pouches of rats were prepared by the Selye procedure (7). Acute exudative inflammation was induced by injecting 1 ml of olive oil containing croton oil (1%) into an air pouch which had been produced by introducing 20 ml of air into subcutaneous tissue on the dorsa of rats; the air was removed 3 days later. AM-833 (10 mg/kg) was intravenously injected into four rats on day 6 of inflammation.

Preparation of assay specimens. Mouse blood samples were taken by decapitation at 0.5, 1, 2, 3, 4.5, and 6 h after oral dosing and 0.17 and 0.33 h after intravenous dosing. Rat blood samples were serially collected at the same times as mouse blood samples through polyethylene catheters in-

* Corresponding author.

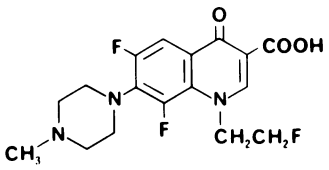

FIG. 1. Chemical structure of AM-833.

serted into the femoral arteries. Blood samples from other species were obtained by venipuncture at predetermined times after dosing: rabbits, 0.17, 0.33, 0.5, 1, 2, 3, 5, 7, and 9 h; dogs, 0.5, 1, 2, 3, 6, 9, 14, 24, 34, and 48 h for oral dosing and 0.08, 0.17, and 0.33 h for intravenous dosing (single dosing) or 2, 4, 6, 8, 24, 26, 48, 50, 72, 74, 96, 98, 100, 102, 104, 120, and 168 h after first dosing (repeated dosing); monkeys, 0.25, 0.5, 1, 2, 3, 6, 9, 12, and 24 h. Serum was separated by centrifugation. For tissue distribution experiments, rats and dogs were sacrificed at the end of infusion by puncture of the abdominal and femoral arteries, respectively, and then blood and brain (rat only), lung, kidney, liver, and spleen tissues were harvested. The tissues were weighed and then homogenized with four times the volume of 1/15 M phosphate buffer (pH 7.0) by using a Polytron homogenizer (Kinematica, GmbH). The homogenate was centrifuged at 2,000 × *g* for 20 min to separate the supernatant. Urine and bile samples of rats were collected through polyethylene catheters inserted into the bladders and common bile ducts, respectively, for 0 to 3, 3 to 6, and 6 to 24 h. Blood, urine, and bile samples of mongrel dogs were taken through polyethylene catheters inserted into the femoral veins, left and right ureters, and common bile ducts, respectively. Blood was taken at 1, 3, 5, 7, 9, 11, 16, and 20 h; urine and bile were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 16, and 16 to 20 h. Granuloma exudate and blood of rats were taken through needles for injection from dorsal pouches at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h. All specimens were stored at −20°C until analyzed.

Protein binding. In vivo protein binding of AM-833 was examined by the ultrafiltration method. From 10 rats given AM-833 orally blood samples were taken at 0.5, 1, 2, 4, and 8 h after dosing, and from five dogs given 100 mg each orally blood was taken at 0.25, 0.5, 0.75, 1, 2, and 6 h after dosing. Serum was separated by centrifugation at room temperature. Portions (5 ml) of serum were loaded on an Amicon Centriflo CF-25 membrane. The concentrations in serum and ultrafiltrate were regarded as the total and unbound concentrations, respectively. The extent of adsorption of AM-833 to the membrane was determined by using 1/15 M phosphate buffer (pH 7.4) containing AM-833 in a range from 0.1 to 8 μg/ml. The binding rate was corrected with the extent of adsorption (8%).

Assay procedure. The high-performance liquid chromatography system consisted of a constant-flow pump (Hitachi model 655 liquid chromatograph), an automated sample injector (Kyowa Seimitsu model KSST-601 autosampler), a variable-wavelength UV detector (Hitachi model 638-41 UV monitor), and a data processor (Hitachi model 833 Chromato-processor).

A sample of a biological specimen (0.1 to 1 ml) was mixed with 0.1 ml of an internal standard solution, 1 ml of 0.5 M phosphate buffer (pH 7.5), and 6 ml of chloroform. The internal standard solution was prepared by dissolving 1-ethyl-6-fluoro-1,4-dihydro-7-imidazol-1-yl-4-oxo-3-quinolinecarboxylic acid in 0.02 N sodium hydroxide (30 to 150 μg/ml). The resulting mixture was vigorously shaken for 5 min and centrifuged at 2,000 × *g* for 5 min, and 5 ml of the chloroform layer was removed and evaporated. The resulting residue was dissolved in 0.1 ml of a mixture (1:1 [vol/vol]) of acetonitrile and 0.04 M phosphoric acid. A sample (5 μl) of the solution was injected into a 4.0 mm (inside diameter) by 25 cm stainless steel column packed with Nucleosil 5 CN (Macherey-Nagel) and equipped with a Nucleosil 5 CN guard column (4.0 mm [inside diameter] by 10 mm). The eluting mobile phase was a 9:1 (vol/vol) mixture of acetonitrile and 0.04 M phosphoric acid. The flow rate was 1.1 ml/min. The wavelength of the UV monitor was set at 287 nm. Calibration standards were prepared by adding 0.1 ml of 0.02 N sodium hydroxide containing AM-833 to 1 ml of blank biological specimen and assaying as described above. The concentration of AM-833 was calculated from the calibration curve constructed by plotting the peak height ratios of AM-833 to the internal standard versus the spiked concentrations of AM-833.

The sensitivity of this procedure was 0.01 μg/ml in serum, urine, and bile and 0.05 μg/g in tissues when 1 ml each of serum, urine, bile, or tissue homogenate was used. Urine and bile were diluted 10 to 100 times with 0.5 M phosphate buffer (pH 7.5). The overall recovery rates of AM-833 from serum and tissues were 85% (at 5.0 μg/ml) and 94 to 97% (at 25 μg/g), respectively. The coefficients of variation were 0.4 and 1.2% at 0.5 and 5.0 μg/ml of serum, respectively, and 0.8 to 4.4 and 0.6 to 1.1% at 2.5 and 25.1 μg/g of tissue, respectively. Peaks of AM-833 and the internal standard were not disturbed by control blank extract. Standard solution of AM-833 was stable for at least 1 week at 4°C. Typical chromatograms are presented in Fig. 2. This procedure provided concentrations of unchanged drug, which were confirmed as follows. A portion of chloroform extract of serum, urine, and bile samples of rats and dogs, which were prepared by the analytical method described above, was developed on a silica gel 60 F_{254} thin-layer chromatography plate (E. Merck) with a mixture of chloroform, methanol, benzene, diethylamine, and water (20:20:10:7:4 [vol/vol]), resulting in one spot of AM-833 alone.

Pharmacokinetic analysis. Results are expressed as the mean and the standard error. The significance of the data

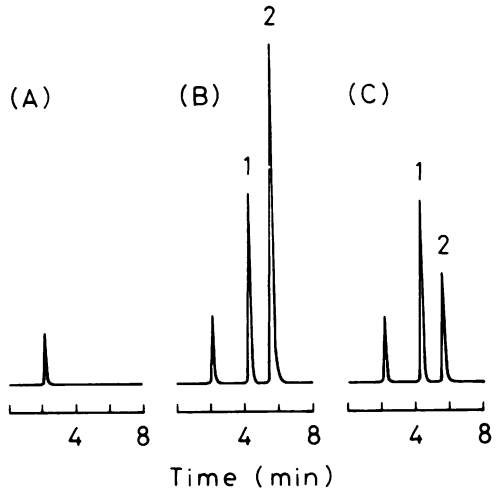

FIG. 2. Typical chromatograms of dog serum. (A) Control dog serum; (B) dog serum spiked with internal standard (peak 1) and 5.05 μg of AM-833 per ml (peak 2); (C) dog serum 1 h after oral administration of AM-833 at a dose of 2 mg/kg.

was evaluated by the Student t test. In species other than mice, pharmacokinetic parameters were calculated from individual concentrations in serum, but in mice individual concentrations in serum were averaged and the mean value thus obtained was used to calculate pharmacokinetic parameters. The serum concentration/time curves after intravenous administration in animals other than monkeys were analyzed by the two-compartment open model, whereas those in monkeys followed one-compartment kinetics. The concentration in serum after oral administration was analyzed by one-compartment kinetics. Pharmacokinetic parameters were obtained as follows. T_{max} was the peak time observed. C_{max} was the peak concentration observed. $t_{1/2}$ was the half-life calculated from the elimination rate constant determined by linear regression analysis. $AUC_{0-\infty}$ was the area under the curve (AUC) calculated as the sum of AUC obtained from zero to the last time by the trapezoidal rule and the ratio of the last concentration measured to the elimination rate constant in the terminal phase. Concentrations in serum during repeated dosing were simulated by using a multiple-dose kinetic equation with a first-order absorption and elimination rate constant based on the one-compartment model.

RESULTS

Levels in serum. Profiles of AM-833 levels in the sera of mice, rats, rabbits, dogs, and monkeys given a single intravenous dose (10 mg/kg) are illustrated in Fig. 3. These animals exhibited a relatively wide species difference in elimination rates (Table 1). Mice, rats, rabbits, dogs, and monkeys showed respective half-lives of 1.95, 2.65 ± 0.07, 1.57 ± 0.11, 9.42 ± 0.20, and 3.45 ± 0.15 h during the elimination phase. On the other hand, these animals showed relatively similar volumes of distribution (V_{ss}): mice, 1.76; rats, 1.30 ± 0.02; rabbits, 1.07 ± 0.03; dogs, 1.28 ± 0.04; and monkeys, 1.21 ± 0.04 liters/kg. These values suggest good

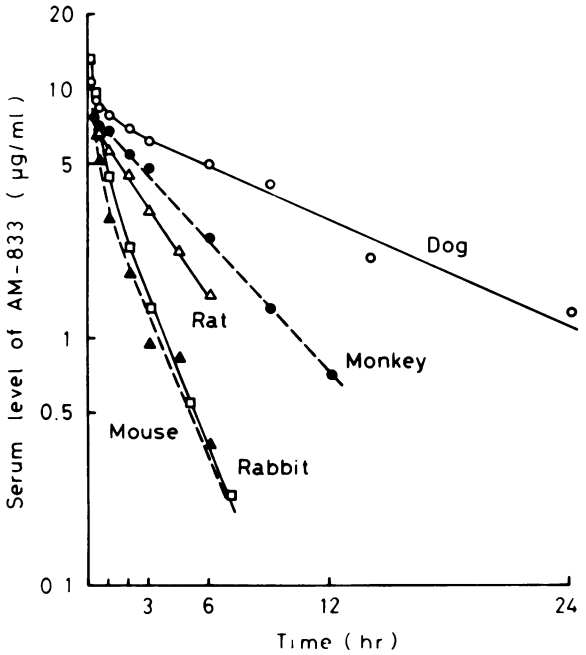

FIG. 3. Mean levels of AM-833 in serum after intravenous injection at a dose of 10 mg/kg in five mice (▲), four rats (△), four rabbits (□), six dogs (○), and three monkeys (●).

TABLE 1. Pharmacokinetic parameters of AM-833 after intravenous injection of 10 mg/kg into mice, rats, rabbits, dogs, and monkeys

Animal (no.)	Parameter[a]		
	V_{ss} (liters/kg)	$t_{1/2\beta}$(h)	$AUC_{0-\infty}$(μg · h/ml)
Mouse (5)	1.76	1.95	12.7
Rat (4)	1.30 ± 0.02	2.65 ± 0.07	28.6 ± 1.1
Rabbit (4)	1.07 ± 0.03	1.57 ± 0.11	16.4 ± 0.9
Dog (6)	1.28 ± 0.04	9.42 ± 0.20	103 ± 4.1
Monkey (3)	1.21 ± 0.04	3.45 ± 0.15	41.3 ± 1.2

[a] V_{ss}, Volume of distribution at steady state; $t_{1/2\beta}$, biological half-life during the elimination phase; $AUC_{0-\infty}$, area under the serum concentration/time curve from zero to infinity. Numbers represent means ± the standard errors.

distribution of AM-833 in the body. In mice, rats, and dogs, levels of AM-833 in serum after an intravenous dose were compared with those after an oral dose (Fig. 4). In mice receiving a dose of 10 mg/kg, the mean AUC values after intravenous and oral (suspension) administration were 12.7 and 10.1 μg · h/ml, respectively. The corresponding values at a dose of 50 mg/kg were 73.4 and 71.4 μg · h/ml. In rats receiving a dose of 10 mg/kg, the mean AUC values were 28.7, 25.4, and 25.8 μg · h/ml after intravenous, oral aqueous solution, and oral suspension administrations, respectively. In dogs receiving a dose of 10 mg/kg, the mean AUC values were 103, 103, and 128 μg · h/ml after intravenous, oral aqueous solution, and oral powder administrations, respectively. The corresponding values at a dose of 2 mg/kg were 26.2, 24.6, and 22.9 μg · h/ml. These results suggest that oral absorption of AM-833 was almost complete in these animals, even if AM-833 was administered as a crystalline powder.

Serial oral administrations of AM-833 to dogs produced gradual increases in levels in serum (Fig. 5) when 2 mg/kg was given twice a day. The level in serum of 2.57 ± 0.17 μg/ml at 2 h after the third dose was 1.54 times higher than the concentration after the corresponding first dose (1.67 ± 0.13 μg/ml) and about equal to that after the ninth dose (2.35 ± 0.12 μg/ml). The respective minimal concentrations on days 2, 3, 4, and 5 were measured as 1.06 ± 0.10, 1.30 ± 0.16, 0.89 ± 0.09, and 0.91 ± 0.09 μg/ml. These values were fairly constant over the experimental period. The solid line in Fig. 5 was obtained by computer simulation using the one-compartment kinetic equation, where parameters were tentatively chosen as follows: an absorption rate constant of 5.00 h^{-1}, an elimination rate constant of 0.080 h^{-1}, and a ratio of the volume of distribution to the absorbed fraction of the dose of 1.20 liters/kg. The good fit suggested that oral absorption of AM-833 was much faster than its elimination from serum. No special accumulation of AM-833 in dogs was postulated based on the good simulation of experimental data with the multiple-dose kinetic equation. This was also supported by the evidence that the elimination half-life (5.36 ± 0.33 h) after the ninth administration was not significantly changed from that (5.90 ± 0.40 h) after the first administration ($P > 0.05$). The C_{max} and AUC of dogs orally given 2, 10, and 40 mg/kg exhibited a dose-related relationship, whereas $t_{1/2}$ values were dose independent (Table 2). These results indicate that linear pharmacokinetic behavior occurs over a dose range from 2 to 40 mg/kg in dogs.

Distribution. From 41 to 57% of AM-833 was bound in rat serum and 41 to 61% was bound in dog serum at total concentrations ranging from 1 to 7 μg/ml. The binding rate was about half of the total AM-833 and virtually independent of AM-833 concentration in the range studied.

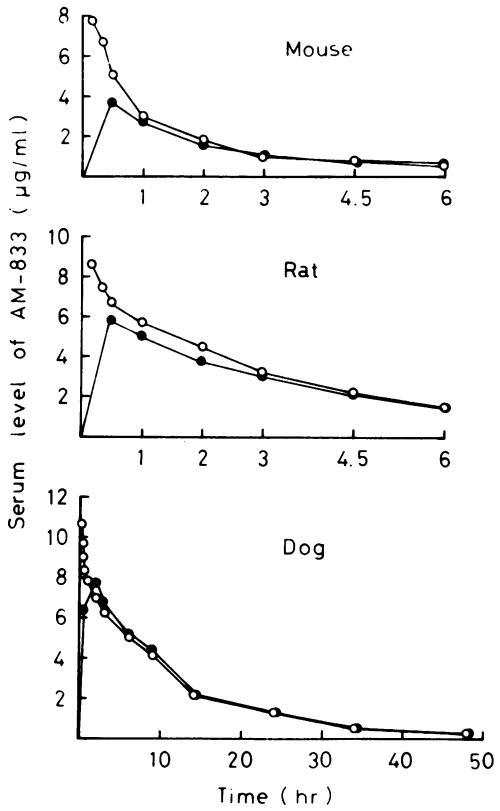

FIG. 4. Mean levels of AM-833 in serum after intravenous (○) or oral (●) administration at a dose of 10 mg/kg in five mice, four rats, and six dogs.

The mean levels of AM-833 in serum and pouch fluid when AM-833 was intravenously injected at a dose of 10 mg/kg into rats with granuloma pouches are present in Fig. 6. The levels in serum decreased to 3.31 ± 0.28 and 0.36 ± 0.03 μg/ml at 2 and 8 h postadministration, respectively. The levels in pouch fluid reached peaks of 2.12 ± 0.09 μg/ml at 4 h postadministration and then decreased more gradually with a half-life of 6.38 h, resulting in levels in pouch fluid four times higher than levels in serum at 8 h postadministration. The mean penetration ratio to pouch fluid ($AUC_{pouch\ fluid}$/AUC_{serum}) was 1.18.

AM-833 levels in brain, lung, liver, spleen, and kidney tissues of rats were measured both at the end of infusion and at 6 h postinfusion. The levels in lung, liver, spleen, and kidney tissues of dogs were determined at the end of constant infusion. Rats showed tissue/serum distribution ratios of 4.2 ± 0.2, 3.1 ± 0.1, 2.3 ± 0.1, 1.1 ± 0.1, and 0.17 ± 0.0 in kidney, liver, spleen, lung, and brain tissues, respectively, at the end of infusion. The respective ratios at 6 h postinfusion were 4.1 ± 0.2, 3.3 ± 0.1, 2.9 ± 0.1, 1.2 ± 0.1, and 0.25 ± 0.02. The distribution ratios in dogs were 3.5 ± 0.0, 2.8 ± 0.2, 2.1 ± 0.1, and 1.6 ± 0.2 in liver, spleen, kidney, and lung tissues, respectively. These results indicate that AM-833 is well distributed among various tissues, but not in brain, and is eliminated from the tissues at rates similar to that of elimination from serum, because there were no significant changes in distribution ratio with time.

Excretion. Excretion of AM-833 urine and bile was examined in rats given a single intravenous or oral dose of 10 mg/kg (Table 3). The peak levels of AM-833 were 430 ± 143 and 310 ± 95 μg/ml in 0- to 3-h pooled urine after intravenous and oral administrations, respectively. The corresponding levels in bile were 46.1 ± 10.2 and 45.5 ± 4.1 μg/ml. The levels in 6- to 24-h pooled urine samples were 120 ± 20 and 115 ± 21 μg/ml after intravenous and oral administration, respectively. The corresponding levels in bile were 24.1 ± 4.4 and 11.0 ± 2.1 μg/ml. The recovery of AM-833 in urine at 24 h postadministration was 42.9 ± 6.8 and 36.2 ± 5.2% of the dose after intravenous and oral administrations, respectively. The respective percentages found in bile were 6.8 ± 1.9 and 5.7 ± 1.2%. Thus, 49.7 and 41.9% of the dose was totally excreted into both urine and bile in 24 h as unchanged AM-833.

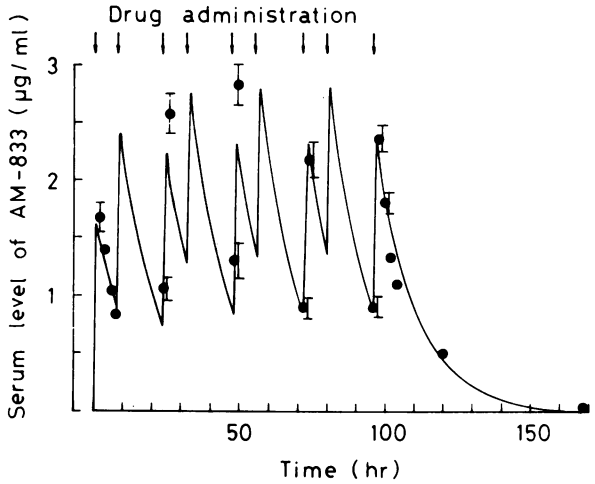

FIG. 5. Mean (± the standard error) levels of AM-833 in serum during repeated oral administration of AM-833 at a dose of 2 mg/kg twice daily for 5 days in three dogs. A simulation curve was calculated based on one-compartment kinetics: absorption rate constant, 5.00 h^{-1}; elimination rate constant, 0.080 h^{-1}; ratio of the volume of distribution to the fraction of the dose absorbed, 1.20 liters/kg.

The levels of AM-833 in serum, urine, and bile were determined in two mongrel dogs given a single intravenous dose of 10 mg/kg (Fig. 7). In this experiment, the dogs were catheterized for collection of urine and bile. The elimination half-lives were 6.06 and 6.40 h, which were shorter than those of intact dogs (Table 1). The levels of AM-833 in urine of dogs were 410 and 548 μg/ml at 0 to 2 h postadministration and about 100 μg/ml at 12 h postadministration. The levels of AM-833 in bile of dogs were 370 and 231 μg/ml at 0 to 2 h postadministration and about 100 μg/ml at 12 h postadministration. Excretion percentages in urine and bile of dogs were 16.0 to 22.7 and 5.3 to 5.7% of the dose, respectively, at 16 h. These results indicated that biliary excretion contributed more to total excretion in dogs than in rats.

TABLE 2. Pharmacokinetic parameters of AM-833 after oral administration in dogs

Dose (mg/kg)	Parameter[a]			
	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)
2	1.47 ± 0.05	1.8 ± 0.3	8.83 ± 0.39	22.9 ± 1.1
10	7.38 ± 0.31	2.8 ± 0.7	10.4 ± 0.51	128 ± 6.6
40	22.5 ± 1.46	2.8 ± 0.2	10.3 ± 0.92	382 ± 36.3

[a] C_{max}, Peak concentration observed; T_{max}, peak time observed; $t_{1/2}$, biological half-life; $AUC_{0-\infty}$, area under the serum concentration/time curve from zero to infinity. Numbers represent means ± the standard errors for six dogs.

DISCUSSION

This study demonstrated that AM-833 was rapidly and completely absorbed from the gastrointestinal tract, moderately bound to serum proteins, well distributed among various tissues except brain, and excreted in urine and bile without accumulation in experimental animals. When AM-833 was given orally, its peak level in dog serum was similar to that of ofloxacin (6, 8) but higher than those of other pyridonecarboxylic acid derivatives (2–5, 9). In experimental animals, precise bioavailability data of other derivatives are not available, but AM-833 exhibited almost perfect systemic availability in mice, rats, and dogs. Good availability of crystalline AM-833 administered orally was also confirmed in dogs. The present study revealed a large interspecies difference in the elimination half-life of AM-833 in mice, rats, rabbits, monkeys, and dogs. Rabbits had the shortest half-life (1.57 h), and dogs exhibited the longest half-life (9.42 h). Animals larger in body weight tended to show a longer half-life of AM-833, but rabbits showed exceptionally rapid elimination of AM-833, suggesting extensive metabolism in rabbits (H. Kusajima, T. Ooie, F. Kawahara, and H. Uchida, J. Chromatogr., in press). AM-833 exhibited elimination rates similar to those of pefloxacin (2) and enoxacin (4, 5, 9) in mice and rats but much slower elimination in dogs compared with known analogs. These observations suggest the possibility of an extended dosage interval of AM-833 in clinical use.

The volumes of distribution of AM-833 were greater than 1 liter/kg in all of the species investigated, suggesting that AM-833 can penetrate into both extracellular and intracellular spaces. This was confirmed by the findings of good penetration into the granuloma pouch and various tissues. The high distribution of AM-833 provides a promising possibility that AM-833 may be useful not only for urinary and biliary tract infections but also for various systemic infections. The levels in tissues of rats declined at rates similar to that in serum, although elimination from brain tissue was slightly slower. Levels in serum during repeated dosing of dogs were well described by the multiple-dose pharmacokinetic equation, and the elimination half-life after the last dose was not significantly changed from that after the first dose. This evidence suggests no accumulation of AM-833 in rats and dogs.

The 24-h recovery percentages of unchanged AM-833 in urine and bile were 42.9 and 6.8% of the dose, respectively,

TABLE 3. Excretion of AM-833 in urine and bile after intravenous or oral administration of 10 mg/kg in rats

Time (h)	Excretion of AM-833[a] in:			
	Urine		Bile	
	Level (μg/ml)	Recovery (% of dose)	Level (μg/ml)	Recovery (% of dose)
Intravenous administration				
0–3	430 ± 143	9.8 ± 4.0	46.1 ± 10.2	1.5 ± 0.6
3–6	340 ± 68	12.3 ± 2.5	52.3 ± 8.6	1.6 ± 0.4
6–24	120 ± 20	20.9 ± 2.8	24.1 ± 4.4	3.8 ± 1.2
0–24		42.9 ± 6.7		6.8 ± 1.9
Oral administration				
0–3	310 ± 95	9.7 ± 2.7	45.5 ± 4.1	2.2 ± 0.5
3–6	302 ± 72	8.4 ± 1.6	32.6 ± 4.9	1.2 ± 0.2
6–24	115 ± 21	18.2 ± 1.0	11.0 ± 2.1	2.3 ± 0.7
0–24		36.2 ± 5.2		5.7 ± 1.2

[a] Numbers represent means ± the standard errors for four rats.

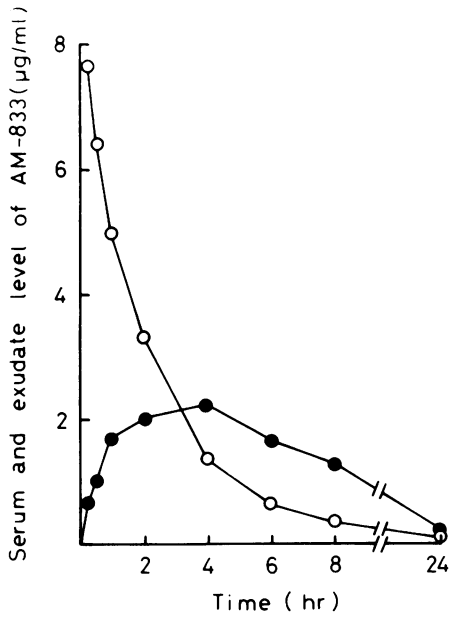

FIG. 6. Mean levels of AM-833 in serum and exudate after intravenous injection at a dose of 10 mg/kg in four rats with granuloma pouches. Symbols: ●, exudate; ○, serum.

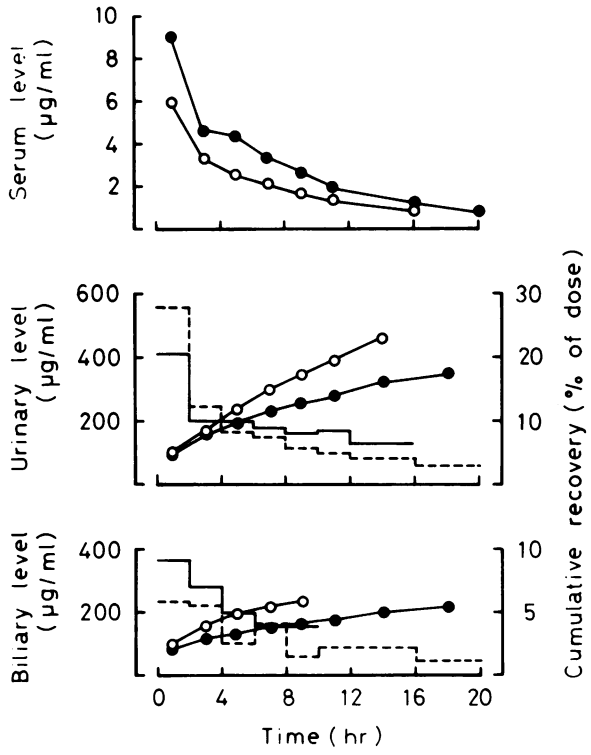

FIG. 7. Levels of AM-833 in serum, urine, and bile and its cumulative recovery in urine and bile after intravenous injection of 10 mg/kg into two mongrel dogs. Open and closed circles represent AM-833 levels in the serum, urine, and bile of dogs A and B, respectively. Solid and broken lines represent recovery of AM-833 from urine and bile of dogs A and B, respectively.

after intravenous administration to rats. The corresponding dog data also cannot account for the complete excretion of AM-833. The evidence suggests some metabolism of AM-833 in rats and dogs (Kusajima et al., in press).

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