ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1983, p. 1-7
0066-4804/83/010001-07$02.00/0

Vol. 23, No. 1

Mechanism of Renal Excretion of AM-715, a New Quinolonecarboxylic Acid Derivative, in Rabbits, Dogs, and Humans

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Received 22 June 1982/Accepted 4 October 1982

The mechanisms of the renal excretion of AM-715, a synthetic antimicrobial agent, were studied in rabbits, dogs, and humans. In both rabbits and humans, AM-715 clearance was greater than creatinine clearance and was profoundly decreased by the administration of probenecid. Thus, in these subjects, AM 715 was cleared by both tubular secretion and glomerular filtration. In dogs, however, the excretion ratio (close to unity), biological half-life, and stop-flow pattern of AM-715 were not affected by probenecid, indicating that the renal excretion of AM-715 took place mostly through glomerular filtration. These results suggest that renal excretion of AM-715 differs with animal species.

AM-715, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, is a new synthetic antibacterial agent with a broad spectrum of activity covering both gram-positive and gram-negative organisms (6, 9). In humans, AM-715 is eliminated predominantly by renal excretion and is metabolized only to a small extent (13). Little is known, however, of the mechanisms by which AM-715 is excreted and, specifically, whether it is actively secreted by the renal tubules in a fashion similar to that of such organic acids as nalidixic acid (7), piromidic acid (7), pipemidic acid (10), miloxacin (7), or cinoxacin (8, 14). The purpose of the present study was to examine the mechanism of renal excretion of AM-715 in rabbits, dogs, and humans. To facilitate this evaluation, AM-715 was administered with and without probenecid.

(This work was presented in part at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy [J. Shimada, Y. Ueda, T. Yamaji, and H. Uchida, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 75, 1980].)

MATERIALS AND METHODS

Renal clearance in rabbits. Five male Japanese White rabbits, weighing 2.8 to 3.4 kg, were used. They were anesthetized with 30 mg of pentobarbital sodium per kg of body weight, administered in the vein of the foreleg. Urine was collected through a cannula inserted in the left ureter. The left femoral artery and auricular vein were catheterized with polyethylene tubes for sampling of blood and administration of drug solution, respectively. A polyethylene catheter was placed in the aorta through the right femoral artery, and blood pressure was monitored by a pressure transducer (type MP-4T; Nihon Koden, Ltd.). The urinary bladder was cannulated for the drainage of accumulating urine. After completion of these surgical preparations by methods described previously (5), an intravenous infusion of 10% mannitol (JP IX; Towa Kasei Kogyo Co., Ltd.) in isotonic saline (solution I) was started at the rate of 1.0 ml/min. When urine flow had stabilized, urine was collected during a 5-min interval, and blood was taken at the midpoint of the interval. Each sample was used as a blank for determining the concentration of inulin, which was injected intravenously through the auricular vein at a priming dose of 40 mg/kg and sustained by the infusion of 0.12% inulin solution in solution I (solution II) at the rate of 1.0 ml/min. After 60 min of the infusion, urine and blood were collected as a blank for the determination of AM-715 concentration. Then, AM-715 was infused at the rate of 0.13 mg/kg per min. The infusion solution was prepared by mixing a 5% aqueous solution of AM-715 (pH 5.0) with solution II. Urine samples were collected during three successive 5-min intervals, beginning 30 min after the start of infusion. Blood samples were taken at the midpoint of urine collections. After these procedures were completed, a single dose of 30 mg of probenecid (GR; Sigma Chemical Co.) per kg was administered intravenously, and urine and blood samples were collected again in a manner similar to that described above.

Renal clearance in dogs. Three male beagles weighing 11.0 to 14.5 kg each were used in this study. The experimental design and procedure were the same as those used in renal clearance experiments in rabbits, except solutions were infused more rapidly (3 ml/min), and three consecutive administrations of solution II containing AM-715 were used at the rates of 0.06, 0.09, and 0.12 mg of AM-715 per kg per min. Beginning 30 min after the infusion of AM-715, urine was collected

TABLE 1. Urinary excretion of AM-715 in rabbits[a]

Treatment	Rabbit no.	Plasma concn of AM-715 (μg/ml)[b]	Urine vol (ml/min)	GFR (ml/min)[c]	AM-715 clearance (ml/min)	AM-715 urinary excretion (μg/min)	AM-715 glomerular filtration (μg/min)	Excretion ratio
Without probenecid	1	3.7 ± 0.3	0.56 ± 0.03	8.3 ± 0.7	31.1 ± 3.1	114.4 ± 4.5	30.6 ± 0.6	3.7 ± 0.1
	2	5.2 ± 0.3	0.56 ± 0.01	7.1 ± 0.6	15.3 ± 1.4	78.4 ± 2.5	36.7 ± 3.0	2.2 ± 0.2
	3	5.2 ± 0.2	0.45 ± 0.02	5.6 ± 0.5	15.0 ± 1.4	77.1 ± 6.6	29.0 ± 1.8	2.7 ± 0.1
	4	6.0 ± 0.3	0.60 ± 0.03	4.5 ± 0.3	12.3 ± 1.0	73.9 ± 3.3	26.7 ± 0.6	2.8 ± 0.1
	5	7.8 ± 0.3	0.58 ± 0.01	3.4 ± 0.3	7.8 ± 0.3	60.6 ± 1.4	26.7 ± 2.6	2.3 ± 0.2
Mean		5.6 ± 0.4	0.55 ± 0.02	5.8 ± 0.5	16.3 ± 2.2	80.9 ± 5.0	29.9 ± 1.2	2.7 ± 0.2
With probenecid	1	7.3 ± 0.1	0.53 ± 0.03	8.6 ± 0.5	9.8 ± 0.3	71.6 ± 1.3	63.3 ± 3.2	1.1 ± 0.1
	2	7.8 ± 0.3	0.56 ± 0.02	7.0 ± 0.1	7.5 ± 0.3	57.9 ± 0.6	54.5 ± 2.8	1.1 ± 0.1
	3	8.3 ± 0.3	0.40 ± 0.03	5.3 ± 0.4	7.3 ± 0.9	59.7 ± 5.8	46.1 ± 1.1	1.3 ± 0.2
	4	10.0 ± 0.5	0.52 ± 0.02	4.0 ± 0.2	5.2 ± 0.6	51.5 ± 3.4	39.7 ± 0.3	1.3 ± 0.1
	5	10.9 ± 0.7	0.50 ± 0.03	2.8 ± 0.2	3.7 ± 0.3	39.6 ± 1.3	29.9 ± 0.5	1.3 ± 0.0
Mean		8.9 ± 0.4	0.50 ± 0.02	5.5 ± 0.6	6.7 ± 0.6	56.0 ± 3.1	46.7 ± 3.2	1.2 ± 0.0

[a] Numbers represent mean ± standard error (n = 3).
[b] No protein binding of AM-715 was assumed.
[c] GFR, Glomerular filtration rate.

three times at 5-min intervals. Blood samples were taken at a midpoint of each 5-min interval. This procedure was repeated for each of the three doses. Then, 30 mg of probenecid per kg was administered intravenously by bolus injection, keeping the infusion rate at 0.12 mg of AM-715 per kg per min. When 30 min had passed, the experimental maneuvers described above were performed.

Stop-flow analysis in dogs. Four male beagles weighing 11.5 to 13.5 kg each were used in this study, which was performed according to the method of Higashio et al. (5). Twenty milligrams of sodium *para*-aminohippurate (PAH; 20% [wt/vol]; Daiichi Seiyaku Co., Ltd.) per kg and 100 mg of creatinine (GR; E. Merck AG) per kg was respectively administered to dogs as a priming dose through the femoral vein. A sustaining solution (15% mannitol–0.9% NaCl–0.25% creatinine–0.2% PAH [solution III]) was then infused at the rate of 3 ml/min. After the urine flow rate became constant, urine and blood samples were collected as a blank for determination of AM-715 concentration. Then, AM-715 was infused at the rate of 0.1 mg/kg per min, using solution III containing AM-715 (solution IV). About 1 h after starting the infusion of solution IV, urine samples were collected twice at 3-min intervals for the determination of free-flow clearance. Blood samples were taken at the same time. The urine flow was then stopped by applying a hemostat clamp to the ureter, and the clamp was removed 6 min later. After the removal of the clamp, the urine was collected serially in 30 0.5-ml test tubes. One minute before removal of the clamp, inulin was intravenously administered at a dose of 25 mg/kg. After completion of the control experiment, 30 mg of probenecid per kg was administered intravenously, keeping the infusion rate of solution IV at 0.1 mg/kg per min. When 30 min had passed, the experimental maneuvers described above were performed.

Effect of probenecid on serum concentration after intravenous injection in dogs. A total of 3.8 mg of AM-715 plus 38.5 mg of PAH per kg was administered intravenously to four male beagle dogs weighing 12.5 to 13.7 kg each. Venous blood samples were taken at 0, 10, 20, 30, 45, 60, and 120 min for assay of the serum concentrations of AM-715 and PAH. Three days later, the same experimental maneuvers were performed in the same dogs, but 30 mg of probenecid per kg was intravenously administered 30 min before the administration of AM-715.

Effect of probenecid on serum concentration and urinary recovery after oral administration in humans. Five male volunteers aged 25 to 41 years and weighing 59 to 79 kg each gave written informed consent to participate in this study. Two hundred milligrams of AM-715 was administered orally with a glass of water. The serum concentration of AM-715 and endogenous creatinine were determined at 0, 0.5, 1, 2, 3, 4, 6, 8, and 12 h after the administration. Urine samples were collected at 0 to 1, 1 to 3, 3 to 5, 5 to 7, 7 to 9, and 9 to 12 h after administration. Two days later, the same trials were performed with the same subjects, but 1 g of probenecid (Probenemid; Nippon Merck Co., Banyu Ltd.) was given orally 30 min before the administration of AM-715.

Analytical procedures. Urine, plasma, and serum samples were stored at −20°C until assayed.

The concentrations of AM-715 in rabbit and dog urine and serum were assayed by high-pressure liquid chromatography as follows. To 1 ml of plasma and diluted urine samples, 2 ml of water and 1 ml of 15% trichloroacetic acid (GR; E. Merck AG) were added. The mixture was shaken well with a mechanical stirrer and centrifuged for 10 min at 3,000 rpm at room temperature. To 3 ml of the supernatant, 0.5 ml of 2 N NaOH and 0.5 ml of acetic anhydride (special grade; Nippon Rikagakuyakuhin Co.) were added. The mixture was allowed to stand in boiling water for 5 min. After cooling, 1 ml of 2 N HCl was added to the

TABLE 2. Urinary excretion of AM-715 in beagle dogs[a]

Treatment	AM-715 infusion rate (mg/kg per min)	Concn (μg/ml) of AM-715 in:		GFR (ml/min)[c]	AM-715 clearance (ml/min)	AM-715 urinary excretion (μg/min)	AM-715 glomerular filtration (μg/min)	Excretion ratio
		Urine	Plasma[b]					
Without probenecid	0.06	57 ± 4	4.6 ± 0.2	25.0 ± 0.7	25.5 ± 1.3	116.5 ± 3.7	115.9 ± 5.7	1.0 ± 0.1
	0.09	107 ± 6	8.7 ± 0.2	22.6 ± 0.8	24.5 ± 0.8	211.6 ± 5.6	195.0 ± 4.4	1.1 ± 0.0
	0.12	156 ± 7	13.2 ± 0.3	20.1 ± 0.8	22.1 ± 0.7	291.8 ± 6.8	266.1 ± 11.0	1.1 ± 0.0
With probenecid	0.12	174 ± 11	15.3 ± 0.3	20.5 ± 0.9	19.4 ± 0.8	296.1 ± 9.3	312.9 ± 12.0	1.0 ± 0.0

[a] Numbers represent mean ± standard error of three dogs.
[b] No protein binding of AM-715 was assumed.
[c] GFR, Glomerular filtration rate.

mixture. AM-715 was extracted from the cooled acidic mixture to 5 ml of dichloromethane (special grade; Nippon Rikagakuyakuhin Co.), and 4 ml of the dichloromethane layer was removed, washed twice with 3 ml of distilled water, and evaporated to dryness. The residue was dissolved with 0.5 ml of a 5:5:1 (vol/vol) mixture of chloroform-methanol–28% ammonia water containing the amine form of AM-715, 7-amino-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, as an internal standard (ca. 2 μg/ml). Samples were chromatographed on a Hitachi model 635A liquid chromatograph at 35°C, using a 150-mm stainless steel column (2.6-mm inner diameter) packed with LiChrosorb Si 100 (5 μm; E. Merck AG). The eluting mobile phase was a 100:150:20:14 (vol/vol) mixture of dichloromethane–acetonitrile–methanol–28% ammonia water. The flow rate was 1.0 ml/min. The column pressure was maintained at 70 kg/cm^2. The spectrophotofluorimeter was set at 300 and 420 nm as excitation and emission wavelengths, respectively. The concentration in each sample was calculated from the appropriate standard calibration curve determined by the least-squares method. The sensitivity of the procedure was 1.0 and 10 μg/ml for plasma and urine, respectively. This procedure gave the concentration of unchanged AM-715 without being affected by metabolites.

Radioisotope (11) and high-pressure liquid chromatography studies (13) have shown that AM-715 undergoes some metabolic alteration but is primarily excreted in unchanged form in both animals and humans. Therefore, a high-pressure liquid chromatography method specific to the unchanged form of AM-715 was used as the assay method in the animal studies. Its sensitivity (detectable limit, 1.0 μg/ml), however, was not enough to determine serum concentration of volunteers receiving 200 mg of AM-715; therefore, bioassay was employed in human studies.

Human samples were assayed with the cup method, using *Escherichia coli* NIHJ JC-2 as the test organism (12). The detectable sensitivity limit of this bioassay method for AM-715 was 0.05 μg/ml. Metabolites of AM-715 did not affect practically the bioassay of AM-715.

For inulin determination, the modified Dische method (3) was used. PAH concentrations were determined by the Bratton-Marshall method (4). Creatinine was measured with an autoanalyzer (model 7060; Hitachi Ltd.) by the improved Jaffe method (1). Sodium and potassium ion were determined by flame photometry (model FPF-2; Hitachi).

Protein binding of AM-715. Protein-binding studies were performed on dog and human plasma, to which ^{14}C-labeled AM-715 was added, with equilibrium dialysis. Samples were dialyzed for 48 h against 0.05 M phosphate buffer (pH 7.4) at 4°C. Unbound ^{14}C-labeled AM-715 was determined by using a liquid-scintillation counter. It was found that the dog-to-human plasma protein-binding ratio was 0 to 5% at an AM-715 concentration of 0.4 to 9.9 μg/ml. Therefore, plasma protein binding of AM-715 was assumed to be negligible for the data analysis.

Data analysis. The glomerular filtration rate (inulin clearance) was obtained from the concentration of inulin in plasma and urine and from the urine volume. The glomerular filtration of AM-715 was calculated by multiplying the plasma concentration of unbound AM-715 by the glomerular filtration rate. The urinary excretion of AM-715 was obtained by multiplying the concentration of AM-715 in urine by the urine volume. The renal clearance of AM-715 was obtained by dividing the urinary excretion by the concentration of AM-715 in plasma. The excretion ratio was calculated by dividing the urinary excretion by the glomerular filtration of AM-715.

Statistical analysis. Results are expressed as the mean ± standard error. The significance of the data was evaluated by the Student t test. A value of $P < 0.05$ was considered significant.

RESULTS

Results in rabbits. Results of renal clearance experiments are shown in Table 1. Each value listed is the mean ± standard error of three determinations in each animal.

The five rabbits showed substantial intersubject variation in the concentration of AM-715 in plasma at 30 min after the start of the infusion of AM-715 without probenecid (3.7 to 7.8 μg/ml), as compared with the variation found in dogs, as described later. Even so, a relatively uniform excretion ratio of 2.2 to 3.7 was obtained which did not depend on plasma concentrations. This high excretion ratio suggests the tubular secretion of AM-715 in rabbits. Probenecid (30 mg/kg) induced a marked reduction in the excretion

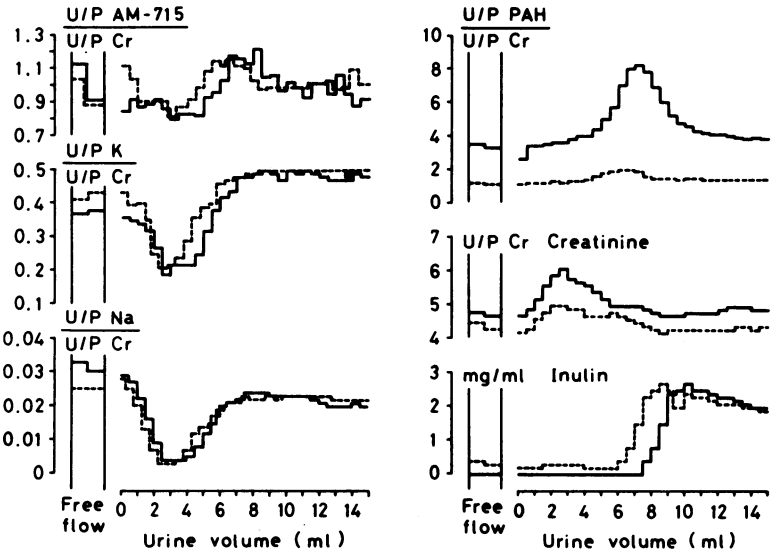

FIG. 1. Stop-flow pattern of AM-715 in dogs. AM-715 was given by a sustaining dose of 0.1 mg/kg per min. ——, Before probenecid; ———, after probenecid.

ratio, from 2.7 ± 0.2 to 1.2 ± 0.0 (Table 1). In no case was there any abnormal change in blood pressure, urine volume, or urinary pH, factors which are generally known to affect the excretion of drugs, throughout the clearance experiment.

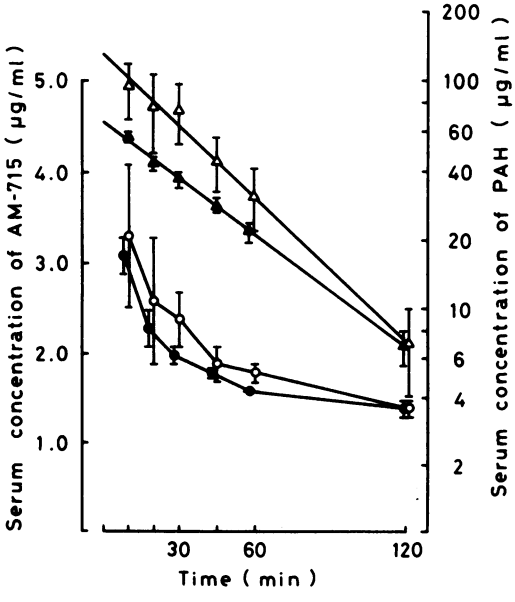

FIG. 2. Mean ± standard error serum concentration of AM-715 and PAH after intravenous coadministration of AM-715 (3.8 mg/kg) and PAH (38.5 mg/kg) without and with probenecid in dogs. ○, AM-715 without probenecid; ●, AM-715 with probenecid; △, PAH without probenecid; ▲, PAH with probenecid.

Results in dogs. Renal clearance studies were performed with three doses of AM-715 without probenecid and with one dose with probenecid. There were three dogs in each experimental group. None exhibited any significant changes in blood pressure, urine volume, or urinary pH during these experiments. The amount of AM-715 excreted into the urine was almost equal to the amount estimated for glomerular filtration of AM-715 (Table 2). The ratio of renal clearance of AM-715 (22.1 to 25.5 ml/min) to that of inulin (20.1 to 25.0 ml/min) was 1.0 to 1.1 and was not dependent on plasma concentration, which ranged from 4.6 to 13.2 μg/ml.

Probenecid (30 mg/kg) had almost no effect on the renal excretion of AM-715. The excretion ratio when probenecid was used was 1.0 ± 0.0 (mean ± standard error of three dogs).

The above results suggest that, in dogs, AM-715 is excreted mostly through glomerular filtration. To further examine the contribution of the renal tubules to the excretion of AM-715, a stop-flow analysis was conducted. Locations of secretion from the proximal renal tubules and of reabsorption through the distal renal tubules were determined, using PAH, and sodium and potassium, respectively, as markers. Inulin was administered as a marker of glomerular urine. The ratio of the concentration of creatinine in urine to that in plasma was used as a parameter of concentration in urine. A typical pattern is shown in Fig. 1. The ratio of the concentration in urine to that in plasma of each component divided by the ratio of creatinine concentration in urine to that in plasma is plotted on the ordinate. No definite peak or trough of AM-715

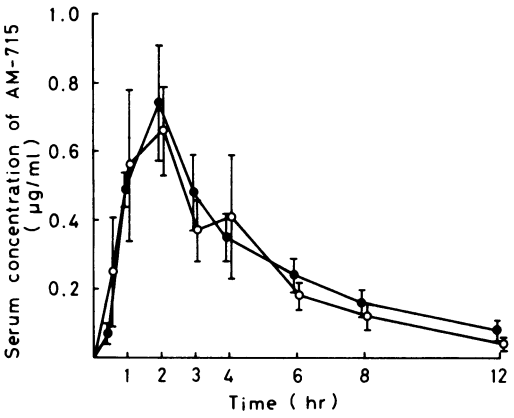

FIG. 3. Mean ± standard error serum concentration of AM-715 after oral administration of 200 mg of AM-715 without (○) and with (●) probenecid in human volunteers.

was found corresponding to the peak of PAH and the trough of sodium and potassium (Fig. 1). With the administration of probenecid, the peak of PAH disappeared, but the stop-flow pattern of AM-715 showed no significant change.

To further investigate whether probenecid inhibits the renal excretion of AM-715 or decreases the volume of distribution, serum concentrations were analyzed pharmacokinetically. Figure 2 shows the mean serum concentrations of AM-715 and PAH after intravenous coadministration. An one-compartment open model was satisfactory to represent serum concentrations of PAH both with and without the administration of probenecid. With the administration of probenecid, the biological half-life of PAH became significantly longer (0.580 ± 0.023 h [mean ± standard error]), as compared with the half-life obtained without the administration of probenecid (0.447 ± 0.036 h). However, a two-compartment open model was needed for the determination of the serum concentrations of AM-715. Pharmacokinetic parameters of AM-715 are shown in Table 3. There were no significant changes in the various parameters, including the volume of distribution of central compartment and the biological half-life, with the administration of probenecid.

Results in humans. Probenecid had no effect on the concentration of AM-715 in serum (Fig. 3). However, urinary recovery of AM-715 for 12 h after oral administration decreased to about one half with the administration of probenecid (Table 4). The mean urinary recovery rate was 28% of the dose without the administration of probenecid and 14% of the dose with the administration of probenecid. Creatinine clearance, AM-715 clearance, and the ratio of AM-715 clearance to creatinine clearance for each time period are shown in Table 4. The clearance ratios for the period from 3 to 5 h and the period from 5 to 7 h were significantly decreased by the administration of probenecid. When subjects received AM-715 alone, the mean clearance ratios were 2.4 and 3.4, but they declined to near unity with the administration of probenecid.

DISCUSSION

In rabbits, the renal clearance of AM-715 was greater than the glomerular filtration rate (inulin clearance), and the ratio was 2.2 to 3.7. Therefore, it can be said that, in rabbits, AM-715 was excreted through both glomerular filtration and tubular secretion. This evidence is confirmed by the results obtained with the administration of probenecid. Administration of probenecid caused a marked decrease of excretion ratio (Table 1). Probenecid is known to be actively secreted by the renal tubules and to block the active secretion of many organic acids by its potent affinity for the carrier for anion transport (2). Renal tubular secretion of pipemidic acid, a dipolar ionic quinolone derivative similar to AM-715, is also competitively inhibited by probenecid in dogs (10). The reduction of the excretion ratio of AM-715 in rabbits with the administration of probenecid could also be due to the same mechanism, owing to the structural similarities of these compounds. The excretion ratio

TABLE 3. Pharmacokinetic parameters of serum level of AM-715 in dogs

Parameter[a]	Treatment[b]	
	Without probenecid	With probenecid[c]
A (μg/ml)	4.60 ± 0.70	3.47 ± 0.32
B (μg/ml)	2.27 ± 0.21	2.12 ± 0.13
α (h^{-1})	8.128 ± 1.893	7.341 ± 0.311
β (h^{-1})	0.240 ± 0.027	0.242 ± 0.032
K_{12} (h^{-1})	5.074 ± 1.534	4.021 ± 0.192
K_{21} (h^{-1})	2.693 ± 0.374	2.966 ± 0.288
K_{el} (h^{-1})	0.697 ± 0.127	0.596 ± 0.053
V_c (liter)	7.50 ± 0.74	9.06 ± 0.56
AUC (μ · h/ml)	10.27 ± 0.77	9.55 ± 0.93
$t_{1/2}$ (β) (h)	3.02 ± 0.42	2.90 ± 0.35

[a] Serum level of AM-715 (C) was represented by $C = Ae^{-\alpha t} + Be^{-\beta t}$, where A, B, α, and β were constant. K_{12}, First-order rate constant of drug transport from the central, immediately permeable compartment to the peripheral compartment; K_{21}, first-order rate constant of reverse drug transport from the peripheral compartment back to the central compartment; K_{el}, first-order rate constant of drug elimination; volume of distribution of central compartment; AUC, area under plasma concentration-time curve from time zero to 12 h; $t_{1/2}$ (β), biological half-life.

[b] Numbers represent mean ± standard error of four dogs.

[c] Not significant ($P > 0.05$).

TABLE 4. Urinary excretion of AM-715 after oral administration of 200 mg of AM-715 in humans

Treatment	Subject no.	Clearance period (h)	Creatinine clearance (ml/min)	AM-715 clearance (ml/min)	Clearance ratio	Urinary recovery (% dose)[a]
Without probenecid	1	3–5	109.2	290.7	2.7	
		5–7	108.2	190.0	1.8	19.9
		7–9	139.9	301.7	2.2	
	2	3–5	100.1	170.0	1.7	
		5–7	146.7	441.2	3.0	23.8
		7–9	147.0	345.1	2.4	
	3	3–5	121.8	225.5	1.9	
		5–7	154.0	501.3	3.3	33.1
		7–9	117.8	359.3	3.1	
	4	3–5	145.0	363.6	2.5	
		5–7	106.2	524.9	4.9	51.9
		7–9	112.6	398.1	3.5	
	5	3–5	82.1	280.0	3.4	
		5–7	161.6	633.6	3.9	11.2
		7–9	111.8	ND[b]	ND	
Mean		3–5	111.6 ± 10.6	266.0 ± 32.6	2.4 ± 0.3	
		5–7	135.3 ± 11.7	387.5 ± 65.3	3.4 ± 0.5	28.0 ± 6.9
		7–9	125.8 ± 7.4	351.1 ± 19.9	2.8 ± 0.3	
With probenecid	1	3–5	146.4	252.6	1.7	
		5–7	140.2	184.2	1.3	10.7
		7–9	131.0	220.0	1.7	
	2	3–5	133.8	160.2	1.2	
		5–7	139.0	141.6	1.0	12.4
		7–9	123.6	216.7	1.8	
	3	3–5	239.1	139.5	0.6	
		5–7	104.0	138.3	1.3	17.4
		7–9	115.7	173.3	1.5	
	4	3–5	101.3	121.6	1.2	
		5–7	104.9	104.0	1.0	20.0
		7–9	102.7	111.5	1.1	
	5	3–5	129.7	150.2	1.2	
		5–7	111.4	153.2	1.4	8.9
		7–9	121.7	187.6	1.5	
Mean		3–5	150.1 ± 23.4	164.8 ± 22.9	1.2 ± 0.2	
		5–7	119.9 ± 8.1	144.3 ± 12.9	1.2 ± 0.1	13.9 ± 2.1
		7–9	118.9 ± 4.7	181.8 ± 19.7	1.5 ± 0.1	

[a] Recovery of AM-715 12 h after administration.
[b] ND, No detectable serum concentration of AM-715.

of AM-715 was close to unity after the administration of probenecid, indicating little contribution of renal tubular reabsorption to renal excretion of AM-715 in rabbits. Miloxacin, an acidic quinolone derivative, has been reported to be reabsorbed through the renal tubules in rabbits (7). From this renal clearance study of AM-715, renal tubular secretion was found to take some part (53 to 73%) in the renal excretion of AM-715 in rabbits.

The excretion ratio of AM-715 in dogs was close to unity, was not dependent on plasma levels of AM-715, and was not altered by administration of probenecid. These results indicate that the renal excretion of AM-715 takes place mostly through glomerular filtration in dogs and that there is little or no contribution from renal tubular secretion and reabsorption. The stop-flow pattern of AM-715 was not affected by probenecid, even under experimental conditions that caused the peak of PAH to disappear with probenecid. The pharmacokinetic parameters of AM-715 after intravenous administration were not affected by administration of probenecid, whereas the biological half-life of PAH was significantly prolonged by the administration of probenecid. These stop-flow and pharmacokinetic data also suggest that the renal tubules make little contribution to the renal excretion of AM-715 in dogs.

In humans, the renal clearance of AM-715 was 2.4 to 3.4 times greater than the creatinine

clearance and was reduced remarkably with the administration of probenecid. Statistical analysis showed that there were significant differences between the ratios of AM-715 renal clearance to creatinine clearance obtained with the administration of probenecid and the ratios obtained without probenecid for the clearance periods of 3 to 5 and 5 to 7 h. The clearance ratios decreased to near unity with the administration of probenecid. From this evidence, it appears that renal tubular secretion is involved in the urinary excretion of AM-715 in humans in addition to glomerular filtration. Pharmacokinetic parameters such as peak concentration and biological half-life were not changed with the administration of probenecid as expected, owing to the large intersubject variation in serum level.

The results of the present study suggest that the renal excretion of AM-715 takes place mostly through glomerular filtration in dogs. In rabbits and humans, however, renal tubular secretion is also involved, in addition to glomerular filtration. These results suggest that the renal excretion of AM-715 differs with animal species.

ACKNOWLEDGMENT

We acknowledge the excellent technical assistance of Kyohei Endo, Mamoru Suekawa, Takeshi Tsuchiya, and Hiroshi Morikawa.

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