Renal Disposition of Moxalactam in Experimental Animals as Revealed by Stop-Flow Analysis

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The mechanisms of moxalactam excretion were studied by stop-flow analysis in dogs, monkeys, and rabbits. In dogs, the amount of moxalactam excreted in the urine was almost equal to that estimated by glomerular filtration. There was no specific moxalactam peak corresponding to the *p*-aminohippuric acid (PAH) peak in the stop-flow patterns of the dogs. The PAH peak disappeared with administration of probenecid, but the moxalactam stop-flow pattern showed no change. In monkeys, no specific moxalactam peak corresponding to the PAH peak could be detected. In the stop-flow pattern of the rabbit, the peak moxalactam concentration corresponded with that of PAH and disappeared with probenecid. These results suggest that in dogs and monkeys renal excretion of moxalactam takes place mostly through glomerular filtration. In rabbits, however, there is a small renal tubular secretory component added to the primary element, glomerular filtration. These observations point to differences in the mechanisms of moxalactam excretion in different animal species.

Moxalactam (latamoxef [6059-S], World Health Organization-approved generic name), a newly developed, injectable, semisynthetic oxa-β-lactam antibiotic (1, 5, 6, 9, 11), has exhibited a longer serum half-life (7, 10) and a lower nephrotoxicity (3) than cephalosporin antibiotics in both experimental animals and humans. The precise renal elimination mechanisms of this compound have not as yet been determined. In the present study, the mechanisms of renal moxalactam excretion by beagle dogs, cynomolgus monkeys, and rabbits have been examined by renal clearance and stop-flow methods.

MATERIALS AND METHODS

Drugs. The contents of a 1-g vial of moxalactam (lot no. F55A 0125050N) were dissolved in 20 ml of 0.9% saline. Inulin (5%), mannitol (10 or 15%), creatinine (10%; Merck & Co.), probenecid (6%, solubilized with NaOH; Sigma Chemical Co.), and sodium *para*-aminohippurate (PAH; 20% solution) were all of special grade.

Animals. Twelve 9- to 10-kg male beagle dogs, bred and raised in the Shionogi Aburahi Laboratories; five female and one male cynomolgus monkeys, weighing 2.6 to 3.7 kg, with normal blood biochemistry profiles; and 11 3-kg male Japanese White rabbits were used in the various studies. During infusion experiments, the urine pH of these animals ranged from 7.1 to 7.5.

Operative procedures. Animals were anesthetized with 30 mg of pentobarbital sodium per kg administered in the vein of the foreleg. After tracheotomy, an incision was made in the left flank. The retroperitoneal space was explored, and the left ureter was cannulated. Urine was collected through the cannula. In the dogs, blood was collected from the right axillary artery, and injection of test compounds and fluid infusion were performed through the right axillary vein. A cannula was also inserted in the right femoral artery, and blood pressure was monitored through a pressure transducer (MP-4T; Nihon Koden) attached to the cannula. In the monkeys, blood was collected from the right femoral artery, and injection of test compounds and fluid infusion were performed through the right femoral vein. In the rabbits, blood was collected from the right carotid artery, and injection of test compounds and fluid infusion were performed through the right lateral jugular vein.

Analysis of urine and plasma samples. Urine and plasma samples were analyzed for creatinine with the Technicon Auto-Analyzer, by the method of Folin, with picric acid color development (2); for inulin with diphenylamine reagent (4); for PAH by the method of Bratton-Marshall (8); and for sodium and potassium by atomic absorption analysis.

Moxalactam in urine and plasma samples was assayed by the band-culture method, with *Escherichia coli* 7437 as the test organism (11).

Renal clearance. Renal clearance was examined in beagles. After the operative procedures, 40 mg of inulin per kg and 1 mg of moxalactam per kg were intravenously injected via the axillary vein as priming doses. Sustaining solution (10% [wt/vol] mannitol–0.9% NaCl–0.12% inulin) was then infused with an infusion pump at the rate of 3 ml per min per dog (ca. 10 kg). Infusion rates of 0.5, 1.0, 2.0, 4.0, and 8.0 mg per kg per h were employed to elevate the blood level of moxalactam in a stepwise manner. At each dose

TABLE 1. Concentrations of total and unbound moxalactam in plasma of beagle dogs under constant intravenous infusion

Dog no.	Moxalactam infusion rate (mg/kg/h)	Plasma moxalactam (µg/ml)		% Binding
		Total	Unbound[a]	
7[b]	5.0	28.1	18.8	33.1
8[b]	5.0	22.8	15.6	31.6
9[b]	5.0	27.5	18.3	33.5
10[b]	5.0	33.8	22.1	34.6
11[c]	8.0	20.3	12.3	39.4
12[c]	8.0	42.4	25.2	40.6

[a] Determined by the ultrafiltration method.

[b] A 15% mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH–moxalactam solution was intravenously infused at a rate of 0.50 ml/min per kg.

[c] A 10% mannitol–0.12% inulin–0.9% NaCl–moxalactam solution was intravenously infused at a rate of 0.30 ml/min per kg.

level, urine was collected for volume determination three times at intervals of 5 min beginning at 30 min after the initiation of infusion. Blood was collected at the midpoint of urine collection. After completing these procedures with all moxalactam doses, 30 mg of probenecid per kg was intravenously administered, and urine and blood samples were again collected as described above.

Stop-flow method. (i) Dogs. Priming doses of PAH (20 mg/kg) and creatinine (100 mg/kg) were intravenously administered via the axillary vein. Sustaining

solution (15% [wt/vol] mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH) was then infused at the rate of 5 ml per min per 10 kg. The priming dose of moxalactam was 10 mg/kg and the sustaining dose was 5.0 mg per kg per h. About 1 h after starting the infusion, when the urine volume became constant (3 to 5 ml per min per 10 kg), we collected two urine samples at 3-min intervals for the determination of free-flow clearance. Blood samples were collected at the same time. The urine flow was then stopped by applying a hemostat clamp to the ureter. The clamp was removed 6 min later. The spurting urine (0.5 ml per sample) was collected in 30 polyacrylic resin tubes. One minute before removal of the clamp, inulin was intravenously administered at a dose of 500 mg per 10 ml per 10 kg.

(ii) Monkeys. The experiment was performed in the same manner as for dogs. However, the priming dose and sustaining infusion were given via the right femoral vein. Urine samples (0.5 ml each) were collected in 20 tubes. Blood was collected from the right femoral artery.

(iii) Rabbits. The priming dose and sustaining infusion were given via the right jugular vein. Urine samples (0.5 ml each) were collected in 20 tubes. Blood was collected from the right carotid artery.

Determination of moxalactam binding to plasma. Protein-bound and free moxalactam were separated by ultrafiltration. A 10-cm section of Visking tubing (seamless cellulose tubing, 6.4-mm diameter) was filled with 1 to 2 ml of plasma, folded in half, put into a polyethylene tube, and centrifuged at 4°C and 1,000 × g for about 20 min. The concentration of the antibiotic in the ultrafiltrate was determined. The percentage of moxalactam binding was calculated as [(plasma con-

TABLE 2. Urinary excretion of moxalactam by beagle dogs[a]

Moxalactam infusion rate (mg/kg/h)	Moxalactam plasma concn (µg/ml)		Urine vol (ml/min)	C_{IN} (ml/min)	Moxalactam		
	Total	Unbound			Unbound C_{MO} (ml/min)	Urinary excretion (µg/min)	Glomerular filtration (µg/min)
0.5	2.9 ± 0.23	1.7 ± 0.14	3.7 ± 0.16	17.9 ± 1.1	21.6 ± 0.9	36.2 ± 2.4	29.3 ± 1.4
1.0	4.3 ± 0.37	2.6 ± 0.22	3.4 ± 0.13	16.4 ± 1.2	17.5 ± 1.0	43.1 ± 2.1	40.9 ± 3.0
2.0	8.0 ± 0.62	4.8 ± 0.37	3.1 ± 0.12	13.5 ± 0.8	14.8 ± 1.1	66.8 ± 1.6	62.4 ± 3.9
4.0	16.7 ± 1.45	10.0 ± 0.87	2.9 ± 0.13	11.7 ± 0.3	12.9 ± 1.1	120.1 ± 4.7	111.6 ± 7.2
8.0	38.9 ± 2.64	23.4 ± 1.59	2.2 ± 0.18	9.8 ± 0.8	9.3 ± 0.5	215.1 ± 18.5	223.6 ± 21.0

[a] Average of four experiments. Values represent mean ± SEM ($n = 4$).

TABLE 3. Effect of probenecid on urinary excretion of moxalactam in beagle dogs[a]

Animal no.	Control phase[b]			Probenecid phase[b]		
	C_{MO} (ml/min)[c]	C_{IN} (ml/min)	Clearance ratio (C_{MO}/C_{IN})[d]	Unbound C_{MO} (ml/min)	C_{IN} (ml/min)	Clearance ratio (C_{MO}/C_{IN})[e]
1	11.2 ± 0.28	10.9 ± 1.10	1.02	9.2 ± 0.07	8.3 ± 0.64	1.10
2	7.1 ± 0.50	5.9 ± 0.30	1.20	5.8 ± 0.70	4.1 ± 0.07	1.44
3	10.0 ± 0.50	10.4 ± 0.13	0.96	7.1 ± 0.37	6.9 ± 0.36	1.03
4	8.8 ± 0.88	11.9 ± 1.19	0.74	9.6 ± 0.63	9.8 ± 0.70	0.98

[a] The moxalactam infusion rate was 8.0 mg per kg per h.

[b] Values represent mean ± SEM ($n = 3$).

[c] The fraction of moxalactam bound to dog plasma was 40%.

[d] Average ± SEM ($n = 4$) was 0.98 ± 0.094.
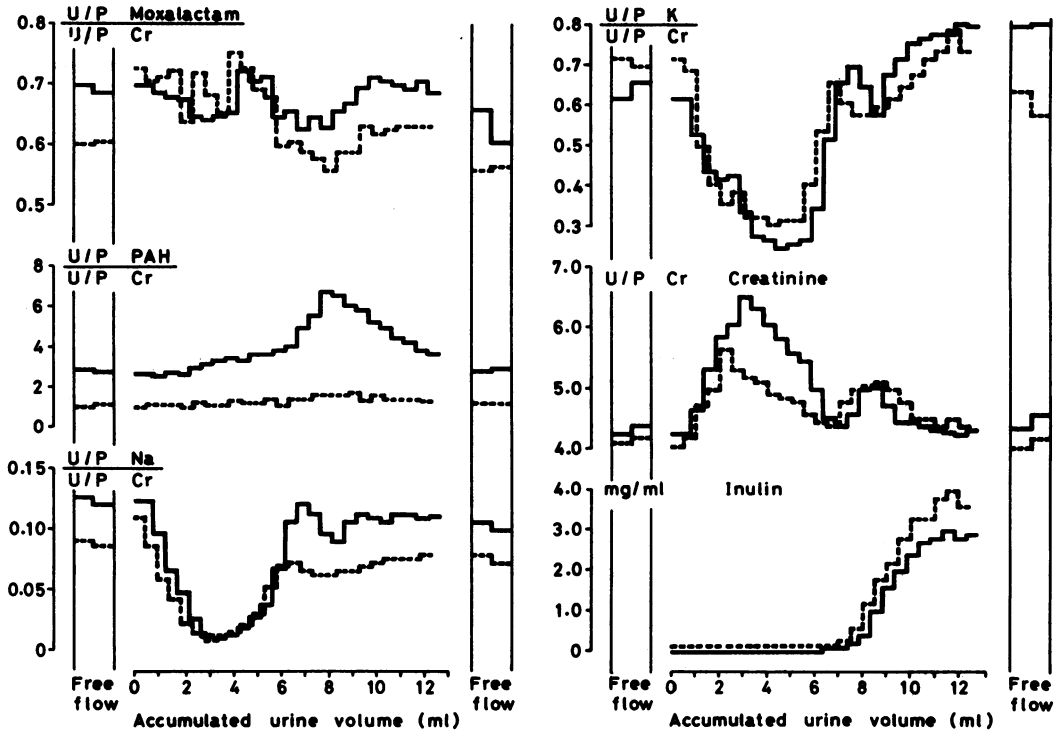
[e] Average ± SEM ($n = 4$) was 1.14 ± 0.103.

FIG. 1. Moxalactam stop-flow pattern in dogs. Moxalactam was given at a priming dose of 10 mg/kg, followed by a sustaining dose of 5.0 mg per kg per h. The experiments were performed with eight animals. ———, Before probenecid; ------, after probenecid. Cr, Creatinine.

centration − filtrate concentration)/plasma concentration] × 100.

RESULTS

Dogs. Plasma binding of moxalactam ranged from 32 to 35% (mean, 33%) with constant infusion of a 15% mannitol–0.9% NaCl–0.25% creatinine–0.7% PAH–moxalactam solution at the rate of 0.50 ml per min per kg. The mean blood level of moxalactam was 28 µg per ml of plasma (Table 1). Plasma binding was 40% with constant infusion of a 10% mannitol–0.12% inulin–0.9% NaCl–moxalactam solution for renal clearance determination (Table 1).

The rate of urinary excretion of moxalactam (micrograms per minute per kidney) and the estimated amount of moxalactam filtered by glomeruli (micrograms per minute per kidney) calculated from the plasma concentration of unbound moxalactam and the glomerular filtration rate (inulin clearance [C_{IN}]), are shown in Table 2. The plasma concentration of unbound moxalactam was calculated with the assumption that plasma binding of moxalactam was 40%. The amount of moxalactam excreted in the urine was almost equal to the amount estimated by glomerular filtration. The renal clearance of unbound moxalactam (unbound C_{MO}) was ob-

tained by dividing urinary excretion of moxalactam by plasma concentration of unbound moxalactam (with the values shown in Table 2). The unbound C_{MO}-to-C_{IN} ratio was 1.08 ± 0.04 (average ± standard error of the mean [SEM] of five dose levels in four dogs). On the other hand, the total C_{MO}-to-C_{IN} ratio was 0.65 ± 0.02 (average ± SEM of five dose levels in four

TABLE 4. Concentrations of total and unbound moxalactam in plasma of cynomolgus monkeys[a]

Monkey no.	Plasma moxalactam (µg/ml)		% Binding[b]
	Total[c]	Unbound[d]	
1	85.6	49.9	41.7
2	62.2	45.8	26.4
3	39.5	27.7	29.1
4	48.5	42.2	13.0
5	32.8	29.0	11.6
6	21.0	16.4	21.9

[a] A 15% mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH–moxalactam solution was intravenously infused at a rate of 0.50 ml/min per kg. The moxalactam infusion rate was 5.0 mg per kg per h.
[b] Average ± SEM was 23.9 ± 4.6%.
[c] Average ± SEM was 48.3 ± 9.4 µg/ml.
[d] Determined by the ultrafiltration method. Average ± SEM was 35.2 ± 5.2 µg/ml.

TABLE 5. C_{MO} in cynomolgus monkeys[a]

Monkey no.	Urine vol (ml/min)	C_{CR} (ml/min)	PAH clearance (ml/min)	C_{MO} (ml/min)		C_{MO}/C_{CR}	
				Total	Unbound	Total	Unbound
1	1.8 ± 0.66	3.6 ± 0.88	12.9 ± 1.89	2.7 ± 0.80	4.7 ± 1.38	0.73 ± 0.05	1.25 ± 0.09
2	1.1 ± 0.03	2.1 ± 0.07	8.5 ± 0.41	1.1 ± 0.03	1.5 ± 0.05	0.51 ± 0.01	0.70 ± 0.01
3	1.6 ± 0.07	3.4 ± 0.07	23.6 ± 0.27	2.7 ± 0.17	3.7 ± 0.10	0.79 ± 0.04	1.11 ± 0.03
4	1.1 ± 0.04	2.6 ± 0.11	14.5 ± 0.36	1.9 ± 0.13	2.2 ± 0.15	0.73 ± 0.03	0.84 ± 0.03
5	2.1 ± 0.15	4.3 ± 0.19	25.7 ± 0.84	3.4 ± 0.27	3.8 ± 0.31	0.78 ± 0.03	0.89 ± 0.03
6	1.7 ± 0.16	4.0 ± 0.25	17.0 ± 0.57	2.9 ± 0.14	3.7 ± 0.17	0.74 ± 0.02	0.94 ± 0.03
Average ± SEM	1.6 ± 0.17	3.3 ± 0.34	17.0 ± 2.67	2.4 ± 0.34	3.3 ± 0.49	0.71 ± 0.04	0.95 ± 0.08

[a] Values represent mean ± SEM ($n = 4$).

dogs). The difference between these two values was statistically significant ($P < 0.05$).

Administration of probenecid (30 mg/kg) had no significant effect on renal excretion of moxalactam (Table 3). At a moxalactam dose of 8.0-mg per kg per h, the C_{MO}-to-C_{IN} ratio was 0.98 ± 0.09 (mean ± SEM of results from four dogs), compared with 1.14 ± 0.10 after probenecid administration.

To assess involvement of the renal tubules in moxalactam excretion, we conducted stop-flow analysis. The location of excretion from the proximal renal tubules was determined with PAH as a marker, and the location of reabsorption through the distal tubules was determined with sodium and potassium. The ratio of urine levels-to-plasma levels (U/P) of creatinine was calculated as a factor of concentrated urine. Figure 1 shows a typical stop-flow pattern. The U/P of moxalactam divided by the U/P of creatinine is plotted on the ordinate. No specific moxalactam peak was present corresponding to the PAH peak, which is the marker of the proximal tubules, or to the sodium trough area,
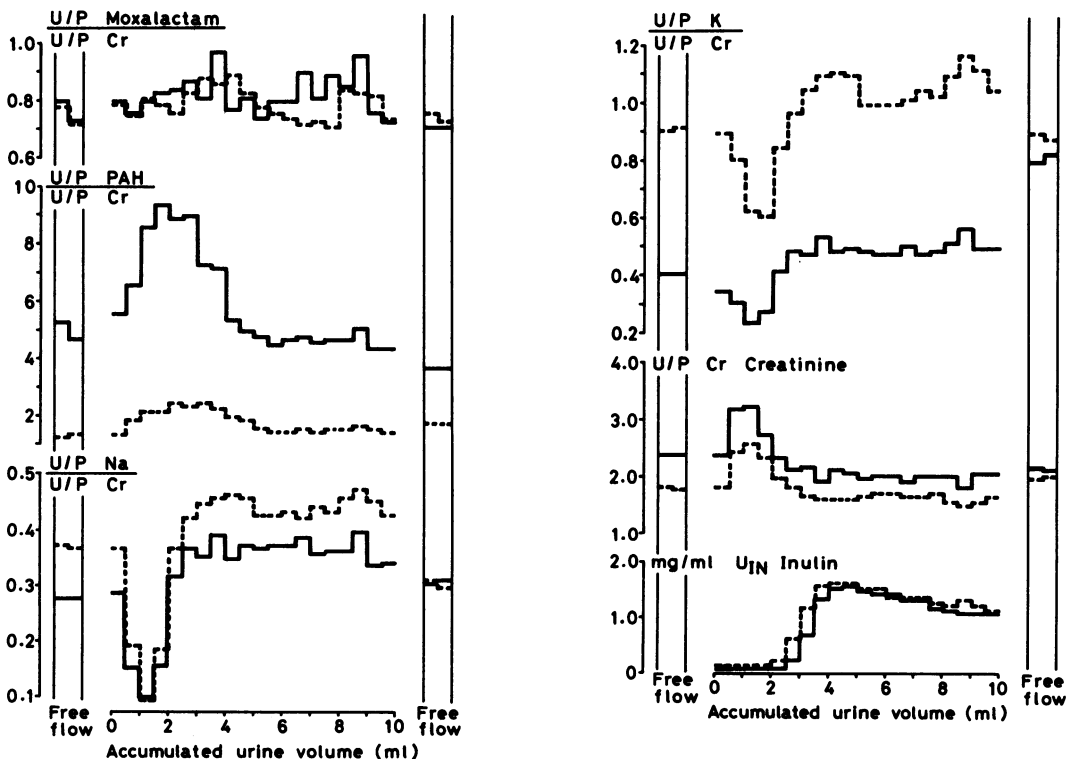

FIG. 2. Moxalactam stop-flow pattern in cynomolgus monkeys. The experiments were performed with six animals at the same moxalactam dose as in the dogs. ———, Before probenecid; ------, after probenecid.

TABLE 6. Concentrations of total and unbound moxalactam in plasma of rabbits[a]

| Rabbit no. | Plasma moxalactam (μg/ml) | | % Binding[b] |
	Total[c]	Unbound[d]	
1	17.7	15.2	14.0
2	10.3	8.9	13.7
3	28.7	22.6	21.3
4	23.5	17.3	26.4
5	24.7	17.5	29.1
6	14.9	11.7	21.5

[a] A 15% mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH–moxalactam solution was intravenously infused at a rate of 0.50 ml/min per kg. The moxalactam infusion rate was 5.0 mg per kg per h.

[b] Average ± SEM was 21.0 ± 2.6%.

[c] Average ± SEM was 20.0 ± 2.8 μg/ml.

[d] Determined by the ultrafiltration method. Average ± SEM was 15.5 ± 2.0 μg/ml.

which represents the distal tubules (Fig. 1). With administration of probenecid, the PAH peak disappeared, but the moxalactam stop-flow pattern showed no change.

Monkeys. The fraction of moxalactam bound to plasma of six cynomolgus monkeys undergoing perfusion with 15% mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH–moxalactam was 23.9 ± 4.6% (average ± SEM) (Table 4). The plasma level of moxalactam was 48.3 ± 9.4

μg/ml (average ± SEM) ($n = 6$). Creatinine clearance (C_{CR}) was 3.32 ± 0.34 ml per min per kidney, and total C_{MO} was 2.44 ± 0.34 ml per min per kidney (average ± SEM; $n = 6$; Table 5). The total C_{MO}-to-C_{CR} ratio was 0.71 ± 0.04 (average ± SEM; $n = 6$). Unbound C_{MO}, calculated from the plasma concentration of unbound moxalactam, was 3.27 ± 0.49 ml per min per kidney (average ± SEM), and the unbound C_{MO}-to-C_{CR} ratio was 0.95 ± 0.08 (average ± SEM) ($n = 6$). The total C_{MO}-to-C_{CR} ratio was less than one ($P < 0.05$). The clearance ratio calculated with unbound C_{MO} was closer to one, and the difference between C_{CR} and C_{MO} was not statistically significant.

Moxalactam showed neither peak nor trough corresponding with the PAH stop-flow pattern (Fig. 2). These findings showed that, under basically similar experimental conditions, moxalactam was excreted into the urine of both cynomolgus monkeys and dogs primarily by glomerular filtration.

Rabbits. Plasma binding of moxalactam in rabbits was 14 to 29% when the animals were perfused with 15% mannitol–0.9% NaCl–0.25% creatinine–0.1% PAH–moxalactam (Table 6). The mean plasma level of moxalactam was 20 μg/ml. C_{CR} under the present experimental conditions was 6.69 ± 0.56 ml per min per kidney (average ± SEM; $n = 6$; Table 7). Total C_{MO} was 8.55 ± 1.07 ml per min per kidney (average

TABLE 7. C_{MO} in rabbits[a]

| Rabbit no. | Urine vol (ml/min) | C_{CR} (ml/min) | PAH clearance (ml/min) | C_{MO} (ml/min) | | C_{MO}/C_{CR} | |
				Total	Unbound	Total	Unbound
1	1.5 ± 0.03	6.3 ± 0.32	25.4 ± 4.70	8.4 ± 0.34	9.8 ± 0.47	1.4 ± 0.02	1.6 ± 0.02
2	1.5 ± 0.06	8.3 ± 0.23	34.5 ± 6.83	12.2 ± 1.20	14.1 ± 1.38	1.5 ± 0.11	1.7 ± 0.13
3	3.0 ± 0.29	5.9 ± 0.47	21.3 ± 0.39	5.6 ± 0.48	7.1 ± 0.61	1.0 ± 0.02	1.2 ± 0.03
4	1.7 ± 0.21	5.5 ± 0.65	23.6 ± 1.64	6.0 ± 0.58	8.1 ± 0.79	1.1 ± 0.03	1.5 ± 0.04
5	2.2 ± 0.34	5.6 ± 0.51	23.0 ± 1.02	8.2 ± 0.21	11.5 ± 0.30	1.5 ± 0.14	2.1 ± 0.20
6	1.5 ± 0.07	8.6 ± 0.48	27.0 ± 0.70	11.0 ± 1.12	14.0 ± 1.42	1.3 ± 0.06	1.6 ± 0.08
Average ± SEM	1.9 ± 0.25	6.7 ± 0.56	25.8 ± 1.92	8.6 ± 1.07	10.8 ± 1.21	1.3 ± 0.09	1.6 ± 0.12

[a] Values represent mean ± SEM ($n = 4$).

TABLE 8. Effect of probenecid on C_{MO} in rabbits[a]

| Rabbit no. | Urine vol (ml/min) | C_{CR} (ml/min) | PAH clearance (ml/min) | C_{MO} (ml/min) | | C_{MO}/C_{CR} | |
				Total	Unbound	Total	Unbound
2	1.0 ± 0.18	3.6 ± 0.56	28.6 ± 3.24	2.6 ± 0.15	4.0 ± 0.23	0.77 ± 0.09	1.15 ± 0.14
7	1.8 ± 0.04	6.9 ± 0.13	20.7 ± 0.69	4.2 ± 0.03	4.6 ± 0.03	0.61 ± 0.01	0.66 ± 0.01
8	1.5 ± 0.04	6.0 ± 0.15	21.0 ± 0.27	3.7 ± 0.13	4.2 ± 1.46	0.62 ± 0.03	0.71 ± 0.03
9	1.4 ± 0.09	5.0 ± 0.17	16.9 ± 0.40	3.7 ± 0.15	4.3 ± 0.17	0.74 ± 0.01	0.87 ± 0.01
10	1.7 ± 0.25	6.8 ± 0.73	23.1 ± 1.85	4.6 ± 0.43	4.9 ± 0.46	0.67 ± 0.01	0.71 ± 0.01
11	1.6 ± 0.05	5.5 ± 0.13	19.3 ± 0.34	4.1 ± 0.09	5.3 ± 0.11	0.75 ± 0.01	0.96 ± 0.01
Average ± SEM	1.5 ± 0.12	5.6 ± 0.51	21.6 ± 1.63	3.8 ± 0.27[b]	4.5 ± 0.19[b]	0.69 ± 0.03[b]	0.84 ± 0.08[b]

[a] Values represent mean ± SEM ($n = 4$).

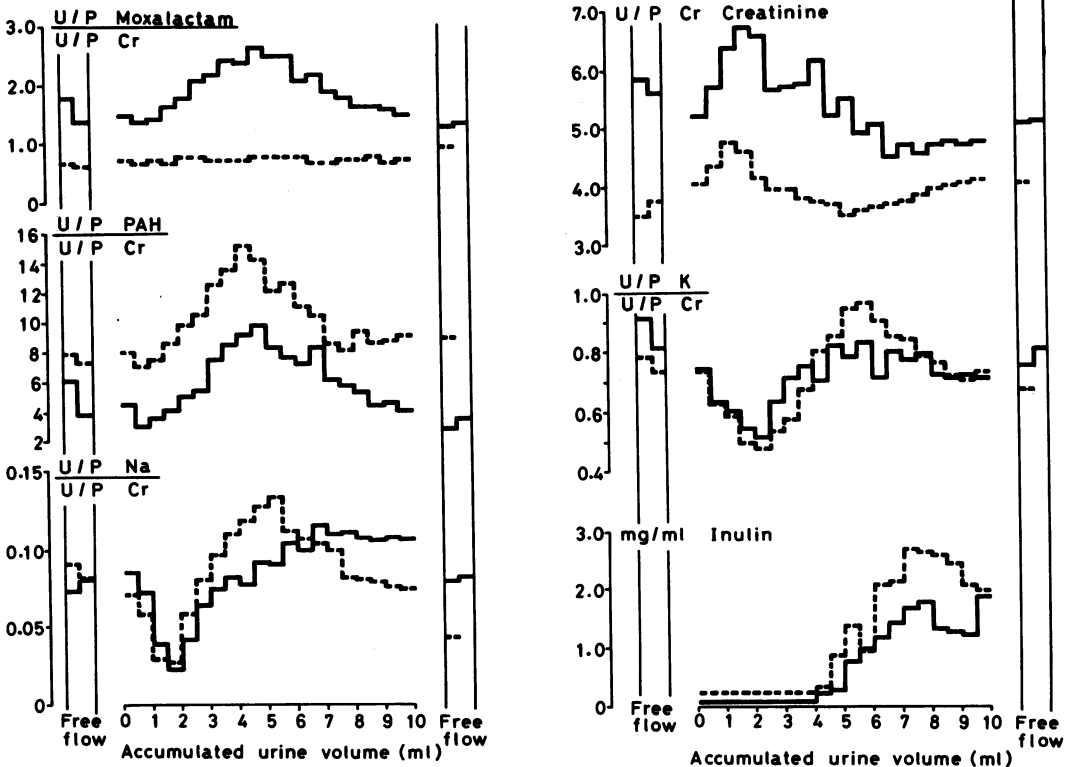[b] Statistically significant at $P < 0.05$ against those of corresponding controls in Table 7.

FIG. 3. Moxalactam stop-flow pattern in rabbits. The experiments were performed with 11 animals at the same moxalactam dose as in the dogs. ——, Before probenecid, ------, after probenecid.

± SEM; $n = 6$), and the total C_{MO}-to-C_{CR} ratio was 1.27 ± 0.09 (average ± SEM; $n = 6$). C_{MO}, obtained with the value of the plasma concentration of unbound moxalactam, was 10.77 ± 1.21 ml per min per kidney (average ± SEM; $n = 6$), and the unbound C_{MO}-to-C_{CR} ratio was 1.61 ± 0.12 (average ± SEM; $n = 6$). Thus, the clearance ratio calculated with unbound C_{MO} was larger than one. Probenecid (30 mg/kg) had a marked effect on C_{MO} in rabbits (Table 8). At a moxalactam dose of 5.0 mg per kg per h, the unbound C_{MO}-to-C_{CR} ratio was 1.61 ± 0.12 (mean ± SEM; $n = 6$ Table 7). It was 0.84 ± 0.08 (mean ± SEM; $n = 6$) with probenecid (Table 8). The difference between these two values was statistically significant ($P < 0.05$).

A typical stop-flow pattern is shown in Fig. 3. The moxalactam peak corresponded with the PAH peak. With administration of probenecid, the moxalactam peak disappeared. This suggested that moxalactam was secreted from the proximal renal tubules in the rabbit.

DISCUSSION

The results of the present study indicate that renal excretion of moxalactam takes place primarily (if not exclusively) through glomerular filtration in beagle dogs and cynomolgus mon-

keys. In rabbits, however, both renal tubular secretion and glomerular filtration were involved in the excretion process. The renal tubular secretion of moxalactam in rabbits might be ascribed to the fact that these animals usually excrete an alkaline urine. This possible relation makes it important to determine whether renal tubular secretion of moxalactam occurs in dogs or monkeys with alkalosis. These results suggest that renal excretion of moxalactam differs with animal species.

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