Effect of Hyperuricemia on Renal Function in the Dog. (30515)

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The relationship of hyperuricemia to renal disease has been poorly understood and often unrecognized. Some investigators believe that the concept of a "gouty kidney" is invalid and, therefore, there is no reason to expect hyperuricemia to be damaging to the kidney. However, it is our opinion that hyperuricemia represents a serious threat to the kidney, not only in gout but also in other hyperuricemic conditions including those associated with irradiation or chemotherapy of neoplasms. Deposition of urates, particularly in the distal convoluted tubules and collecting ducts, contributes to the development of gouty nephritis and is a potential hazard to any kidney exposed to hyperuricemia from any cause. Evidence in dogs and rats to support this concept was reported(1). The present communication on studies of renal function in dogs subjected to induced hyperuricemia supplies additional evidence.

The few available reports on the effects of uric acid on the kidneys of animals are concerned primarily with the gross and microscopic pathologic findings; they do not describe the effects on renal function(2-4). In this study the effects of hyperuricemia on the canine kidney were assessed by determination of renal clearances of creatinine and para-aminohippurate before and at specified intervals after intravenous injection of uric acid.

Materials and methods. Trained female dogs (mongrel and Dalmatian) weighing 7 to 17.4 kg were used. To promote an adequate urinary flow, water (50 ml/kg) was given to each dog by gastric tube 1 hour prior to performance of the clearance tests. A flexible Foley catheter was anchored firmly in the bladder, and urine was collected for specific periods. To ensure complete emptying of the bladder at the end of each collection period, the animal was held upright, the abdomen was massaged, and the bladder was filled with air.

A solution of creatinine (2%) and para-aminohippurate (0.2%) in distilled water was infused continuously through a flexible, fine, polyethylene tube in one of the leg veins at the rate of 80 ml per hour, after an initial priming injection of 30 ml of the same mixture in 1 minute. Collections for clearance studies were begun 40 to 50 minutes after start of the infusion, to permit equilibration of infused substances and establishment of an adequate urinary output. The volume, specific gravity (by hygrometer), and osmolality (freezing-point depression) of the urine collected during each 20-minute clearance period were measured. Blood samples, drawn from the jugular vein into a heparinized syringe, were taken at the beginning and end of each clearance period. Plasma was separated by centrifugation. Para-aminohippurate was determined by the method of Smith and co-workers(5) and creatinine, by the method of Kingsley and Schaffert(6).

Uric acid, prepared by the method of Schade and Boden(7) and determined by the uricase method of King and Wootton(8), was dissolved (35 mg/ml) in a warm saturated solution of lithium carbonate and administered into a peripheral vein over a period of 30 to 90 seconds. The concentration of saturated lithium carbonate solution was approximately 190 mEq/liter and the pH varied between 7.6 and 8.0. This solution without uric acid was given to 2 dogs and proved innocuous to kidney function.

Renal clearances of creatinine and para-aminohippurate were determined before and on various days after a single injection or a series of injections of uric acid. The dogs were divided into 7 groups as shown in Tables I, II and III.

Results. Table I demonstrates that a single injection of uric acid at a dosage of 40 mg/kg produced no change in renal clearance of

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TABLE I. Effect of Single Intravenous Injection of Uric Acid on Renal Clearance in Intact Dogs.

Group	Dose (mg/kg)	Clearance test	Clearances (ml/min/kg)* PAH M1†	M2	M3	M4	D1†	D2	Creatinine M1†	M2	M3	M4	D1†	D2
1	40	Before uric acid	16.9	12.2	12.4	11.3	10.9	16.7	5.8	3.9	3.9	3.3	3.8	3.4
		1 day after	17.3	11.1	14.4	11.8	10.4	17.3	6.2	4.0	4.8	2.7	3.9	3.3
2	100	Before uric acid	13.3	13.1	—	—	10.9	16.7	3.6	3.8	—	—	3.8	4.3
		1 day after	—	10.8	—	—	10.9	14.9	—	2.7	—	—	3.7	4.1
		3 days "	11.1	11.7	—	—	—	—	2.5	3.9	—	—	—	—
		5 " "	13.8	—	—	—	—	—	3.8	—	—	—	—	—

* Values shown as means of 3 or 4 separate determinations; S.E. were about 10% of mean in all cases.

† M indicates mongrel; numbers correspond to same dog within groups but not between groups. D indicates Dalmatian; same dogs were used in both groups.

creatinine or para-aminohippurate. Also, there was no change in blood concentration of urea in either the mongrel or the Dalmatian dogs. Similarly, a single injection of uric acid at 100 mg/kg did not significantly change the clearances of creatinine or of para-aminohippurate in either of the Dalmation dogs (Group 2, Table I). In 2 mongrel dogs, this dose of uric acid led to a significant temporary decrease in clearance of both substances (Table I); the urinary flow was temporarily reduced immediately following injection of uric acid. No change occurred in blood concentration of urea in any of these dogs.

Daily injections of uric acid (40 mg/kg) for 10 days in the 4 mongrel dogs of Group 3 produced temporary decreases in clearances of creatinine and para-aminohippurate (Table II). The clearances were returning toward normal on the fifth day (3 dogs) and eighth day (one dog) after the last injection of uric acid. The blood urea levels, which were below 30 mg per 100 ml in all 4 dogs before receiving uric acid, increased to 60 to 70 mg by the tenth day of urate administration; however, these values returned to control levels within a few days. Dog 4 of Group 3 was killed, during the first day of the recovery period, for histologic study of the kidneys. Of the 4 mongrel dogs in Group 4 which received daily injections of uric acid at 100 mg/kg for 10 days, 2 died within 24 hours after the final injection; hence, postinjection clearances could not be determined. The blood urea levels were increased to about 350 mg per 100 ml at death. Clearances of creatinine and para-aminohippurate in the 2 surviving dogs were initially diminished (Table II). Dog 2 of Group 4 died on the third day after cessation of injections and had a blood urea level greater than 400 mg per 100 ml. Dog 1 was killed for histologic study of the kidneys on the first day of the recovery period.

Two mongrel dogs (Group 5) which had

TABLE II. Effect of 10 Repeated Intravenous Injections of Uric Acid (Once Daily) on Renal Clearance in Intact Dogs.

Group	Daily dose (mg/kg)	Clearance test	Clearances (ml/min/kg)* PAH 1†	2	3	4	Creatinine 1	2	3	4
3	40	Before uric acid	14.2	13.1	13.3	13.0	3.3	3.8	3.6	3.3
		1 day after	11.1	8.6	9.6	9.5	2.7	3.3	2.9	2.8
		5 days "	13.6	12.2	9.4	—	3.2	3.3	3.2	—
		8 " "	—	—	12.5	—	—	—	3.2	—
4	100	Before uric acid	12.6	11.6	—	—	3.9	4.0	—	—
		1 day after	6.1	3.7	—	—	2.5	1.0	—	—

* Values shown as means of 3 or 4 separate determinations; S.E. were about 10% of mean in all cases.

† All are mongrel dogs; numbers correspond to same dog within groups but not between groups.

TABLE III. Effect of Single Intravenous Injection of Uric Acid on Clearance in 3 Dogs 2 Months After Unilateral Nephrectomy and One Dalmatian with Chronic Pyelonephritis.

Group	Dose (mg/kg)	Clearance test	Clearances (ml/min/kg)* PAH 1†	PAH 2	PAH 3	Creatinine 1	Creatinine 2	Creatinine 3
5‡	40	Before uric acid	10.8	13.2	—	3.0	3.8	—
		2 days after	9.8	12.9	—	3.3	3.5	—
6‡	100	Before uric acid	13.3	10.8	12.9	3.6	3.3	3.8
		1 day after	8.4	9.1	10.1	2.3	2.2	2.8
		5 days "	12.8	9.6	9.4	3.4	2.8	2.6
		8 " "	—	9.2	13.0	—	2.9	3.5
7	40	Before uric acid	10.0	—	—	2.8	—	—
		5 days after	5.0	—	—	1.3	—	—
		18 " "	10.1	—	—	3.4	—	—

* Values shown as means of 3 of 4 separate determinations; S.E. were about 10% of mean in all cases.

† All are mongrel dogs except in Group 7; numbers correspond to same dog within groups but not between groups; the single dog in Group 7 was a Dalmatian with chronic pyelonephritis.

‡ Unilateral (left) nephrectomy was performed 2 months before this test.

had unilateral nephrectomy exhibited no significant change in renal clearances of creatinine or para-aminohippurate after a single injection of uric acid at 40 mg/kg (Table III). Three mongrel dogs (Group 6) which had had unilateral nephrectomy showed temporary decrease in clearance of creatinine and para-aminohippurate after a single injection of uric acid at 100 mg/kg (Table III). These values were similar to those produced by the same injection in mongrels with 2 kidneys (Group 2). One Dalmatian dog (Group 7) with renal impairment secondary to chronic pyelonephritis was given a single injection of uric acid at 40 mg/kg. Blood urea and creatinine values were increased and clearances of creatinine and para-aminohippurate were reduced markedly and stayed low for several days (Table III).

Discussion. Uric acid injected intravenously into dogs in doses of 40 mg per kilogram of body weight produces plasma urate levels of about 20 mg per 100 ml in Dalmatian dogs and 13 mg in mongrel dogs; these values return to preinjection levels within an hour in the mongrel dogs and after several hours in the Dalmatian. Doses of 100 mg per kilogram produce higher levels and are sustained longer(9). The present findings clearly indicate that at these levels of hyperuricemia, impairment of renal function can occur. The degree of impairment was increased by the higher dosage and by repeated injections. It was greater in dogs with unilateral nephrectomy or chronic pyelonephritis. The kidney of the mongrel dog possibly showed higher susceptibility to damage than did that of the Dalmatian.

Obstruction by urate crystals deposited distally in the convoluted and collecting tubules could well account for the depression of clearances of both creatinine, which reflects primarily glomerular filtration, and para-aminohippurate, which is eliminated chiefly by tubular cells. Direct evidence to support such a concept was obtained in histologic studies in gouty patients(10), in hyperuricemia patients with lymphoma(11-14), and in animals(1,3,4,9). The renal lesions resulting from the induced hyperuricemia of these studies have been reported. The main feature was that blockage by urates led to dilatation of the glomeruli and the tubules and to some cellular desquamation and flattening of the epithelium(1). Changes were greater in those dogs which received the larger urate doses. Decreased renal clearances of inulin and para-aminohippurate have been found in hyperuricemic patients with leukemia; these clearances were restored to normal by measures directed toward increasing the solubility of uric acid in the kidney(15).

Single injections of uric acid at 40 mg/kg may have produced some renal impairment which could not be detected by the technics employed in this study, since the cumulative effect of a series of such injections did cause decreased clearances of creatinine and para-

aminohippurate. Hyperuricemia may initiate a cycle in which the nephrotoxic effects of excess urates in the blood gradually produce detectable impairment of renal function, thereby rendering the afflicted kidney more susceptible to further damage from hyperuricemia and less able to excrete the excess uric acid. Under certain circumstances, it is possible that uricosuric therapy, which increases the urate content in the distal tubules, might be harmful.

Summary. Renal function in dogs, as assessed by the clearances of creatinine and para-aminohippurate, was impaired by hyperuricemia induced by intravenous injections of uric acid. The degree of functional impairment was related to dosage and to frequency of injection and was possibly aggravated by the presence of renal disease. It was more severe in mongrel than in Dalmatian dogs. Small doses, which singly produced no detectable functional impairment, caused renal damage after repeated daily injections, indicating a cumulative effect. The findings suggest that hyperuricemia may produce significant nephropathy by urate blockage of the distal convoluted and collecting tubules. Such hyperuricemic nephropathy, reversible up to a certain point, may become chronic or fatal if permitted to continue unchecked.

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Changes in Platelet Volume Produced by Temperature, Metabolic Inhibitors, and Aggregating Agents.* (30516)

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Platelets circulate in the blood stream in the form of thin discs(1,2,3); they retain this shape *in vitro* for several hours when citrated blood is kept at 37°C. Aggregation produced by chilling(4), thrombin, or adenosine diphosphate (ADP)(5,6), is accompanied by a change in shape of platelets from discs to spheres with irregular surfaces and a variety of protruding processes(1,3,7,8). The relationship between platelet shape and aggregation is further suggested by the observation

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