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Thiosulfate Pharmacokinetics in Normal and Anuric Dogs (41430)

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Abstract. Cyanide (CN) toxicity has recently become increasingly a clinical problem with the greater use of Laetrile for cancer treatment and of sodium nitroprusside for blood pressure control. Sodium thiosulfate is an excellent antidote for CN toxicity but not all aspects of its pharmacokinetics have been adequately studied. Applying a specific thiosulfate assay, we measured endogenous thiosulfate, the response to CN infusion, and disappearance after iv injection in normal and anuric dogs. Endogenous plasma concentration was approximately 1 mg/dl; the bile concentration was 15 times higher but biliary excretion accounted for less than 2%, compared to renal excretion. Cyanide infusion decreased endogenous plasma thiosulfate 33% before death. The fast component of the thiosulfate disappearance curve was similar, 3 min, after iv injection (150 mg/kg), while the second component was markedly prolonged in anuric dogs (239 min) compared to controls (47 min). Therefore, a constant infusion of thiosulfate would appear to be the best method of maintaining the high plasma concentration necessary for CN detoxification during the continuous administration or absorption of CN-producing compounds.

Thiosulfate has been used as an antidote for cyanide (CN) poisoning for over 47 years (1). In the past, most cases of CN toxicity were associated with either suicide or occupational hazards. Recently, more cases of CN toxicity have resulted from the increased use of sodium nitroprusside and from Laetrile therapy. Sodium nitroprusside is widely used for controlled hypotension during surgery and for reducing afterload in many hypertensive syndromes as well as in clinical congestive heart failure. The major metabolite of nitroprusside is cyanide (2), and toxicity and death from cyanide poisoning have been reported following its prolonged use or administration in large doses (3, 4). Laetrile (amygdalin), of which CN is also a principal metabolite, has been reported to cause toxicity and death, presumably from CN poisoning (5–7), when taken orally for the prevention or treatment of cancer. Thiosulfate has been proposed for prevention of nitroprusside toxicity (8) but adequate information concerning its pharmacokinetics has not been available.

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Cyanide is detoxified in the body by reaction with enzyme rhodanese (thiosulfate: cyanide sulfurtransferase, EC 2.8.1.1) and a sulfur donor that results in the formation of less toxic thiocyanate (9). Rhodanese has been isolated from many organ tissues and is in especially high concentration in the liver; the quantities present are sufficient to convert many times the lethal dose of CN to thiocyanate (10). Thus, the rate-limiting factor in this reaction appears to be the availability of a sulfur donor. Thiosulfate has been shown to act as a sulfur donor both *in vitro* (11) and *in vivo* (1) and also provides a good substrate on which to isolate rhodanese by affinity chromatography (12) but the endogenous sulfur-containing substrate for rhodanese is unknown. Thiosulfate has been isolated from the urine of experimental animals (13) and it appears to be a normal metabolite in higher animals (14, 15). However, the factors that control its formation or utilization are not entirely understood. Vassel and associates (16) showed that dogs excreted thiosulfate as long as they were fed, but if food was withheld, the excretion in the urine ceased. This implied that the availability of thiosulfate was determined by its presence, or the presence of its precursors, in food, and its *de novo* production is probably related

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to metabolism of sulfur-containing amino acids (17). Consequently, nutritional status may be an important factor in the available thiosulfate pool in the body's ability to detoxify CN.

The present study was undertaken to measure the endogenous thiosulfate concentration in plasma, urine, and bile in anesthetized dogs with the application of a thiosulfate-specific assay; concentrations were measured in response to CN administration. In addition, we measured the plasma half-life and volume of distribution of thiosulfate, injected at the therapeutic dose for CN toxicity, in normal and anuric dogs. From these data we were able to calculate the endogenous thiosulfate pool available for CN detoxification.

Methods. Mongrel dogs, 15 to 25 kg, were maintained in the animal quarters for at least 2 weeks prior to the experiment, on a 12-hr photoperiod. They were fed a professional feeder diet (Promix Dog Food; Wayne) which contained 0.3% methionine and 0.32% cystine (percentage of total diet) according to the manufacturer's analysis.

Group I: Thiosulfate clearance. On the day of the experiment, the dog was anesthetized with pentobarbital, 30 mg/kg iv, endotracheally intubated, and mechanically ventilated with room air to maintain P_aCO_2 at 35 ± 2 mm Hg before the start of the experiment. Catheters, placed in the abdominal aorta via the femoral artery and in the femoral vein, were used for pressure measurements and blood sampling. The abdomen was opened by a midline incision and catheters were placed in the common bile duct and the ureters. Electromagnetic flow probes were placed on both renal arteries. Samples of blood, urine, and bile were collected to measure endogenous thiosulfate concentrations. The dog was hydrated with 500 ml of Ringer's solution iv to increase urine flow. Then, a priming dose of creatinine was given as a bolus, 3.5 ml/kg of a 2% solution in saline iv, followed by a constant infusion of the same solution at 0.7 ml/min for the remainder of the experiment. Creatinine clearance (urine concentration × urine flow/plasma concentration) was used as an index of glomerular filtration rate (GFR). After a 45-min equilibration period, two 10-min renal clearances were measured with midpoint arterial blood samples taken. Sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$; molecular weight = 248.11; reagent grade, Fisher Chemical Co., St. Louis, Mo.), 150 mg/kg dissolved in 50 ml of saline (154 mEq NaCl, Travenol, Morton Grove, Ill.) just prior to injection, was injected iv. Blood samples (5 ml) were collected at 2, 5, 8, 10, 15, 20, 30, 60, and 90 min in heparin, while urine and bile samples were collected at 10-min intervals and their volumes were recorded; blood volume was replaced with Ringer's solution (Travenol). Mean blood pressure (MBP) was measured with a Statham P23Db transducer and renal blood flows were measured with Narco flowmeters. Recordings were made on an E for M oscillographic recorder. Hematocrit was measured by the micromethod and creatinine was determined on a Technicon SMAC System by the Jaffe method. Standard renal clearance formulas were used to calculate thiosulfate clearance and excretion rates (18).

Group II: Thiosulfate clearance in anuric dogs. Dogs were anesthetized as before and blood samples were taken to determine the baseline concentrations of thiosulfate, BUN, creatinine, sodium, potassium, and Hct. Under sterile conditions the abdomen was opened by a midline incision and both ureters were tied. The incision was closed and the animal allowed to recover. Blood samples were collected on each of the next three postoperative mornings. On the third postoperative day (72 hr after the initial surgery), the dog was reanesthetized, intubated endotracheally, and mechanically ventilated similarly to Group I dogs. Catheters were placed in the femoral artery and vein and in the common bile duct while flow probes were placed on the renal arteries. No urine collections or renal clearances were done. After a 45-min stabilization period, thiosulfate, 150 mg/kg in 50 ml of saline, was injected iv, and arterial blood samples were collected as before, plus an additional sample at 16 hr after the thiosulfate injection. MBP, heart rate, ECG, renal blood flow, and blood gases and pH were also measured over the 16-hr interval.

Group III: Endogenous thiosulfate me-

tabolism during cyanide infusion. Dogs were anesthetized with pentobarbital, 30 mg/kg iv, endotracheally intubated, and ventilation was adjusted until P_aCO_2 stabilized at 35 mm Hg before the start of the experiment. Tidal volume and ventilation rate were not altered after the start of the experiment. One femoral artery was cannulated for blood pressure measurements; both femoral veins were cannulated for drug infusions and for blood samples, and a Foley catheter was placed in the bladder. Baseline samples and measurements were taken. The animal then received an infusion of potassium cyanide (KCN) at a rate of 0.05 mg/kg/min. Blood and urine samples, pressure recordings, and blood gas measurements were done at 10, 30, 60, and 90 min after the start of the infusion. Blood samples were analyzed for thiosulfate, thiocyanate, CN, and methemoglobin concentrations; urine was analyzed for homocysteine and thiosulfate concentrations.

Thiosulfate analysis. Previously, thiosulfate had been measured by the starch-iodometric titration method of Brun (19), as modified by Dixon (20). This method involved reducing a blue amylose–iodine complex to its colorless components by thiosulfate or, in fact, any reducing substance, e.g., sulfide, present in solution. Since this method was tedious and nonspecific, we investigated other procedures and found a method that had previously been utilized to measure trace amounts of thiosulfate in photographic films, plates, and archival quality prints (21). In this method, thiosulfate was reduced by a borohydride reagent to a sulfide radical that reacts with oxidized *N,N*-dimethyl-*p*-phenylenediamine to form methylene blue. The absorbance of the blue color (665 nm) was measured spectrophotometrically and the concentration of thiosulfate was calculated from a linear curve. This method was reported to measure only thiosulfate and not other sulfur compounds that would otherwise react with the starch–iodine complex. The lower limit of sensitivity was 1 μg/ml and the coefficient of variation (*cv*) for repeated measurements on the same sample (10 μg/ml standard; $N = 15$) was 5.08%.

Thiocyanate and methemoglobin were measured by standard spectrophotometric procedures and CN was measured in whole blood by the microdiffusion method (22). Data were compared by one-way analysis of variance for repeated measurements in the same subject (23) when significance was observed at the 0.05 level of probability. Data were fitted to a double exponential equation using a programmable calculator, and the fit was confirmed by the tail-subtraction method (24).

Results. The thiosulfate assay, done on 22 heparinized plasma samples obtained from 11 normal, unanesthetized, mongrel dogs on 2 successive days was found to be 1.192 ± .117 mg/dl (mean ± SE). The variability was quite large between dogs, with a *cv* of 44%, but within each dog it was more consistent, not varying more than 0.1 to 0.2 mg/dl (10 to 20%) from day to day.

In Group I ($N = 5$), the endogenous thiosulfate concentration was 1.31 ± 0.24 mg/dl in (arterial) plasma, 16.1 ± 4.2 mg/dl in bile, and 1.50 ± 0.35 mg/dl in urine. Two minutes after the iv injection of thiosulfate, 150 mg/kg, the plasma concentration was 177 ± 39 mg/dl, and by 10 min after the injection the plasma level had decreased to nearly one-half this amount, 86.1 ± 12.7 mg/dl (Fig. 1); the bile concentration was 20.0 ± 6.7 mg/dl at this time. At 20 min, the plasma level had decreased to one-third the 2-min concentration and the bile concentration was 24.0 ± 6.9 mg/dl. By 90 min, the plasma level was only 17% of the maximum (2 min) level and though the bile concentration had doubled, total biliary excretion accounted for less than 2% of the injected dose.

The renal clearance of endogenous thiosulfate was less than 2 ml/min (Fig. 2). When exogenous thiosulfate was injected iv in normal dogs, the clearance increased until it was equal to the GFR as measured by the creatinine clearance (Fig. 2). Thiosulfate produced a diuresis with a 50% increase in urine flow during the first 10 min; then flow returned to baseline levels. Renal excretion of thiosulfate increased rapidly after the injection. By 90 min, over 41% of the injected thiosulfate had been excreted (Fig. 2).

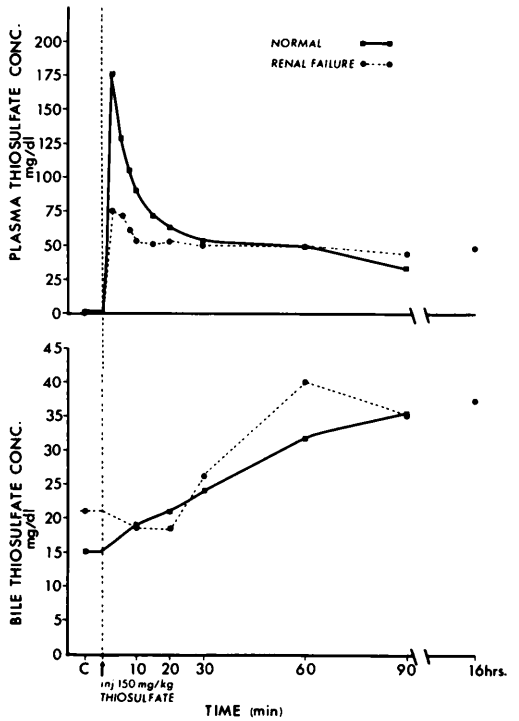

FIG. 1. Plasma (upper) and bile (lower) concentrations in normal and anuric dogs after iv injection of thiosulfate (150 mg/kg) at arrow.

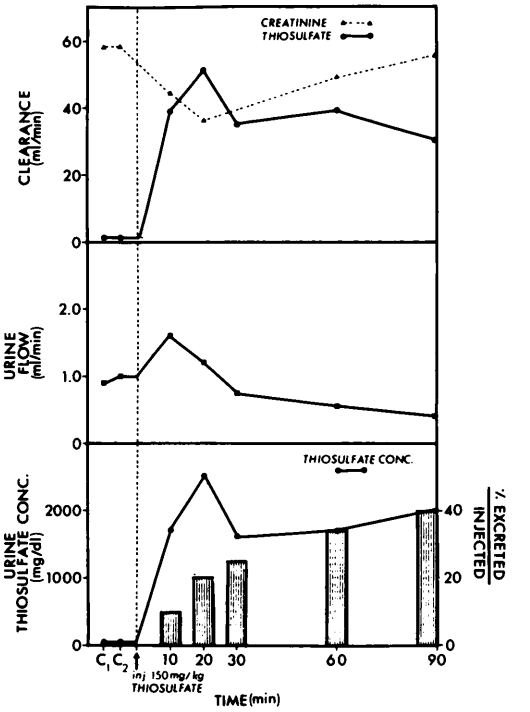

FIG. 2. Clearance of creatinine and thiosulfate (upper graph), urine flow (middle graph), and urine thiosulfate concentration and percentage of injected dose excreted (lower graph, left and right ordinate), respectively, in normal dogs after iv injection of 150 mg/kg.

Blood pressure and heart rate remained constant during and after the injection of thiosulfate in the normal dog while renal blood flow increased from 225 to 275 ml/min (Table I), and then returned to baseline levels after 60 min.

In Group II (N = 4), the endogenous thiosulfate level was slightly higher than in Group I, and remained elevated as the renal failure syndrome progressed over the next 3 days (Table II). At the time of the acute experiment 72 hr after the surgery, the endogenous thiosulfate concentration in the bile was higher in the renal failure dogs than in the normal dogs (Fig. 1). Endogenous creatinine and BUN were elevated as well (Table II). When thiosulfate was injected

TABLE I. EFFECTS OF THIOSULFATE ON RENAL BLOOD FLOW (RBF), MEAN ARTERIAL BLOOD PRESSURE ($\overline{ABP}$), AND HEART RATE (HR) IN NORMAL AND ANURIC DOGS (N = 5)

	RBF (ml/min)		$\overline{ABP}$ (mm Hg)		HR (beats/min)	
	Normal	Anuric	Normal	Anuric	Normal	Anuric
Control	225 ± 36	242 ± 34	129 ± 2	126 ± 6	171 ± 4	166 ± 14
Inject thiosulfate, 150 mg/kg iv						
5 min	275 ± 50*	241 ± 34	127 ± 4	129 ± 8	168 ± 3	152 ± 4
60 min	232 ± 44	250 ± 60	121 ± 5	124 ± 5	160 ± 4	155 ± 9

Note. Results are means ± SE.
* $P < 0.05$ compared to control.

TABLE II. PROGRESS OF RENAL FAILURE SYNDROME FROM DAY 1 WHEN URETERS WERE TIED TO DAY 4 WHEN EXPERIMENT WAS PERFORMED ($N = 4$)

	Day 1	Day 2	Day 3	Day 4
Thiosulfate (mg/dl)	1.94 ± .63	1.48 ± .32	2.73 ± .38	1.74 ± .21
Creatinine (mg/dl)	.93 ± .11	7.20 ± 1.33*	7.70 ± .96*	13.37 ± .48*
BUN (mg/dl)	12.74 ± .96	89.25 ± 17.58*	99.75 ± 15*	178 ± 9.87*

Note. Results are means ± SE. Normal dogs; thiosulfate = 1.19 ± .12 mg/dl.
* $P < 0.05$ compared to Day 1.

into the renal failure dogs the plasma concentration increased and then rapidly decreased within the first 10 min (Fig. 1). Then, the plasma thiosulfate concentration plateaued at 42.3 ± 13.6 mg/dl and remained at this value over the remainder of the period, up to 16 hr after injection. The bile concentration was similar to that in normal dogs after 90 min and did not increase significantly at 16 hr; total biliary excretion of thiosulfate accounted for less than 2% of the injected dose. Renal blood flow, mean arterial blood pressure, and heart rate did not change after injection of thiosulfate in this group (Table I).

The plasma disappearance curves for thiosulfate for the two groups were plotted on semilog graphs and the curves were fitted to a double exponential equation (Fig. 3). Rate constants and half-lives were derived from the equations, and the plots were extrapolated to derive the volumes of distribution for the two groups. After the bolus injection, thiosulfate left the plasma at a rapid rate in both the normal and renal failure dogs, with half-lives of 3.4 and 3.3 min, respectively. The volume of distribution in the anuric dogs was 394 ml/kg while the volume of distribution in the normal dogs was 195 ml/kg. The second component of the disappearance curve in the normal dogs had a half-life of 46.8 min (Fig. 3), while the second component in the renal failure dogs was markedly prolonged, with a half-life of 239 min.

In Group III ($N = 5$), when CN was infused at 0.05 mg/kg/min, the endogenous plasma thiosulfate concentration increased slightly, from 1.04 ± 0.10 to 1.11 ± 0.07 mg/dl (Fig. 4). Plasma thiosulfate concentration then steadily declined to 0.66 ± 0.03 mg/dl at 82.5 ± 8.54 min after the CN infusion was begun. Since this was the average time of death, this final plasma concentration probably represents the lower limit of thiosulfate that is effective in CN detoxification. CN concentration in whole blood increased steadily during the infusion (Fig. 4). Thiocyanate and methemoglobin were below the limits of detection.

Discussion. We have found the methylene blue method for thiosulfate superior to the starch–iodine titration method because of the specificity for thiosulfate, sensitivity to 1 μg/ml, simplicity with no endpoint that may be missed as in titration assays, and no need for deproteinization. We found that the assay could be run directly on plasma and urine without prior treatment. The method had good reproducibility when adequate laboratory techniques were followed.

The dog was chosen as the animal model in which to study thiosulfate metabolism because it appears to have approximately the same lethality for CN as humans do (25, 26), and therefore, we assumed that the dog has similar detoxification capabilities, though this assumption has been questioned by some authors (27). Since little is known about the mechanisms that control thiosulfate metabolism, and because of the increased use of nitroprusside for deliberate hypotension during anesthesia (28), we decided to study thiosulfate metabolism to gain information that would suggest a good method of prophylactic thiosulfate administration when clinical situations might warrant high doses and prolonged administration of nitroprusside.

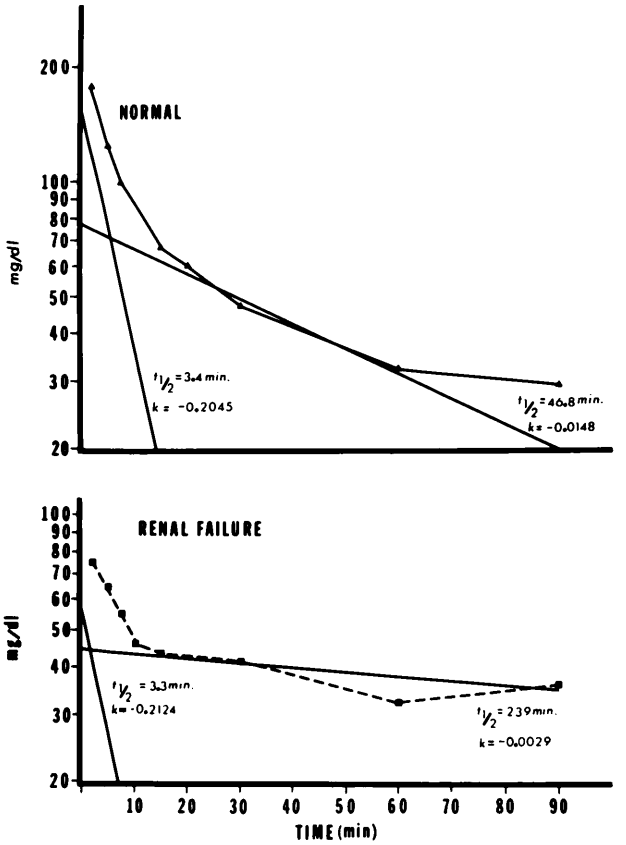

FIG. 3. Plasma thiosulfate disappearance curved for normal (upper) and anuric (lower) dogs plotted on semilog coordinates.

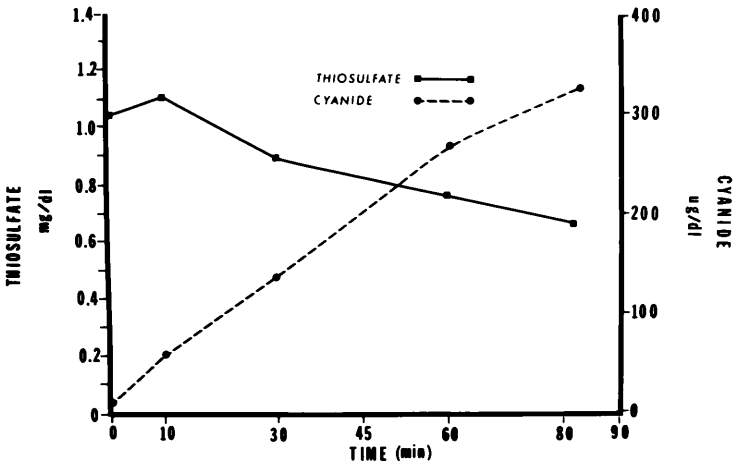

FIG. 4. Plasma thiosulfate concentration (left ordinate) and whole blood CN concentration (right ordinate) during CN infusion (0.05 mg/kg/min).

The extracellular thiosulfate pool can be estimated from our data. The volume of distribution of thiosulfate is equivalent to the extracellular space only if corrections are made for the rapid renal excretion (29). In anuric dogs with a protracted extracellular space and little fluid turnover, thiosulfate distribution apparently is a good measure of this space. In the normal dog, the thiosulfate space was found to be approximately 20% of the body weight, which is in good agreement with previous measurements based on the renal clearance of thiosulfate (29), but is probably a low estimate of the actual extracellular space (18). Using the values of 20% of body weight, a plasma concentration of 1 mg/dl, and a Gibbs–Donnan equilibrium factor of 0.9, a 70-kg man has approximately 155 mg or 1.38 mmole of thiosulfate in the extracellular space.

Cyanide absorption into body tissues may be a relatively slow process, 1½–2 hr, as from red cell stores with nitroprusside (3) or from the gut in the conversion of Laetrile (7) compared to the 47-min half-life of thiosulfate. These situations may require additional exogenous thiosulfate replacement for detoxification, with fluid replacement to avoid dehydration as a result of the osmotic diuretic effect of thiosulfate. Since rhodanese is a mitochondrial enzyme and thiosulfate is poorly permeable to the cell membrane, exogenously administered thiosulfate must greatly exceed the normal plasma concentration to be an effective substrate for rhodanese. Previous studies, in this laboratory (7, 25) as well as in others (26, 30), have shown that a constant infusion of thiosulfate was necessary to provide protection against cyanide lethality during an infusion of either CN or nitroprusside in both dog and man. The results of the present study show that thiosulfate quickly leaves the plasma compartment and is rapidly eliminated by the kidney. Hence, a constant infusion of thiosulfate would appear to be the best method of maintaining the high plasma concentration of thiosulfate necessary for CN detoxification.

Cyanide administration resulted in metabolism of about one-third of the endogenous extracellular thiosulfate. The remaining plasma thiosulfate, 0.6 mg/dl, was apparently below the concentration necessary for effective CN detoxification, probably because of inefficient intracellular transport to the mitochondrial site of the rhodanese. As a result, the CN concentration increased to lethal levels while the plasma thiosulfate concentration did not decrease below this level.

In summary, our study shows that thiosulfate is present in dog plasma at a concentration of approximately 1 mg/dl. The bile concentration is 15 times higher but total biliary excretion accounts for less than 2% of the total excretion. An iv injection of a therapeutic dose of 150 mg/kg (for CN toxicity) is rapidly cleared from the plasma, with a half-life of about 3 min. The major part of the injected dose is eliminated by renal excretion within 90 min, i.e. two half-lives, for disappearance from the extracellular fluid (ECF) compartment. This substance has negligible cardiovascular effects but does increase urine flow and renal blood flow in normal dogs. During renal failure, the endogenous plasma thiosulfate concentration is increased, the metabolic clearance rate is drastically reduced, and after an iv injection, the thiosulfate concentration remains elevated in the plasma for a prolonged period of time, at least 16 hr. A previous study by Tinker and Michenfelder (31) has shown that anuric dogs have an increased resistance to nitroprusside-induced CN toxicity. The present study suggests that the increased resistance results from the absence of renal excretion of endogenous thiosulfate, its consequent accumulation in the ECF, and probably in the intracellular fluid as well, which thus provided additional available thiosulfate for CN detoxification.

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