

Increased Resistance to Nitroprusside-induced Cyanide Toxicity in Anuric Dogs

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Sodium nitroprusside (SNP) is frequently used to decrease afterload in patients who have vasoconstriction with low cardiac output. Often, these patients are concomitantly oliguric or anuric, conditions suggested to be likely to increase the risk of SNP-induced cyanide (CN) toxicity. Previously, the authors determined in normal dogs that SNP, 0.5 mg/kg/hr, was tolerated for 48 hours without CN toxicity, whereas 0.75 mg/kg/hr resulted in toxicity and death. In the present study, dogs rendered anuric by bilateral ureteral ligation were again maintained for 48 hours or until death in a simulated intensive-care situation, and were given various doses of SNP. CN toxicity, as evidenced by near-linear increases in blood CN, metabolic acidosis, and increases of mixed venous blood P_{iO_2} with time, did not occur in animals given SNP at either 0.5 or 0.75 mg/kg/hr ($n = 8$), and was the cause of death in only two of seven dogs given SNP, 1.0 mg/kg/hr. In all five dogs given SNP 1.25 mg/kg/hr, cyanide toxicity developed, with death occurring at an average of 21 hours. Comparisons between the anuric dogs studied herein and the normal dogs studied previously with SNP, 1.0 mg/kg/hr, indicated that CN levels were significantly higher in the normal dogs at 36 hours and that thiocyanate (SCN) levels were significantly lower in the normal dogs at 24 and 36 hours. The observed resistance to SNP-induced CN toxicity in anuric dogs was probably secondary to decreased sulfate and thiosulfate excretion, resulting in greater availability of thiosulfate donor, which in turn enabled greater rates of detoxification of CN to SCN to be catalyzed by hepatic rhodanase. It is concluded that anuria *per se* does not increase the risk of SNP-induced CN toxicity, probably because of increased availability of endogenous sulfur donor. Based on this study in dogs, the authors would not arbitrarily decrease SNP dosage limits in anuric or oliguric patients because of the possibility of cyanide toxicity. (Key words: Anesthetic techniques: hypotension, induced, nitroprusside. Complications: cyanide toxicity. Kidney: anuria; oliguria; failure. Toxicity: cyanide.)

THE BREAKDOWN of sodium nitroprusside (SNP) into cyanide (CN) and the resultant potential for toxicity are generally recognized. CN is normally detoxified to thiocyanate (SCN) by hepatic rhodanase, requiring a sulfur donor (usually thiosulfate).¹ The resulting thiocyanate is excreted in the urine. The rate and extent of detoxification are largely determined by availability of sulfur donor.² We recently reported that normal dogs tolerated chronic SNP doses of 0.5 mg/kg/hr or less for at least 48 hours without CN toxicity. Doses

of SNP of 0.75 and 1.0 mg/kg/hr produced fatal CN toxicity within 36 hours. The latter toxic effects could be avoided by simultaneous administration of thiosulfate (6–12 mg/kg/hr) even when SNP doses were increased to 1.5–2.0 mg/kg/hr.²

It has been suggested that renal failure with oliguria might alter the toxicity of SNP by decreasing the capacity for SCN excretion. This was supported by a recent case report in which increased blood CN above that expected from the administered SNP dose developed in an oliguric patient.³ This concern is clinically relevant, because SNP is often administered to critically ill patients, in whom oliguria or anuria may be a complicating factor. We therefore carried out the present study in a manner nearly identical to that of our previous study, except that the animals were rendered anuric by bilateral ureteral ligations prior to initiation of the SNP infusion. Surprisingly, instead of finding a decreased tolerance to SNP, we observed the opposite.

Methods

Twenty-six fasting unmedicated mongrel dogs weighing 9–11 kg were studied in groups of three in a simulated intensive-care situation. Anesthesia was induced with halothane, 1 per cent, in nitrous oxide, 50–70 per cent, and oxygen. Endotracheal intubation was facilitated with succinylcholine, 20–40 mg, iv. Ventilation was controlled with a Harvard pump to maintain P_{aCO_2} at 36 ± 2 torr (mean \pm SEM). In each animal, a femoral artery and vein were cannulated to monitor arterial pressures, for blood sampling, and for drug and fluid administration. In 24 dogs, bilateral ureteral ligations were performed, via a laparotomy, approximately 3–5 cm from the renal pelves. The kidneys were examined for the presence of double ureters or other abnormalities. Two control animals were subjected to the same laparotomy, but without ureteral ligation. Following the surgical procedure, halothane was discontinued, and the animals were maintained for 48 hours or until death in an intensive-care environment, breathing nitrous oxide, 70 per cent, in oxygen via Harvard pumps. Muscle paralysis was maintained with pancuronium, 0.1 mg/kg given every two to four hours.

Intensive care consisted of the following: body

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Received from the Department of Anesthesiology, Mayo Clinic and Mayo Medical School, Rochester, Minnesota 55901. Accepted for publication June 14, 1979. Supported in part by grants GM 24531 and NS 7505 from the National Institutes of Health.

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temperature (esophageal thermistor) was maintained at 37.5 ± 0.4 C (SEM) with heat lamps or ice packs as needed; penicillin G, 600,000 units, and bicillin, 200,000 units, were given intramuscularly after induction of anesthesia; the lungs were hyperinflated hourly with tracheal suctioning as needed; and the inspired oxygen concentration was adjusted to keep Pa_{O_2} values above 100 torr. Pilot studies were done to determine proper fluid maintenance, because of the anuric state. As in our previously studied normal dogs,² a regimen of 2.5 ml/kg/hr of dextrose, 5 per cent, in saline solution, 0.45 per cent, was well tolerated, but only when the inspired gas was not humidified in the anuric dogs. This total included the volume of flush solutions used to maintain patency of monitoring lines, plus the volume of SNP solution administered. This resulted in reasonably constant plasma sodium concentrations and stable pulmonary-artery wedge pressure values, without fluid overload or hypotension. Hemoglobin concentration gradually decreased, because of repeated blood sampling. Cross-matched donor blood was transfused as needed to maintain hemoglobin concentrations above 11.0 g/dl. The animals were continuously attended.

Control and four-hourly measurements included whole blood cyanide (CN) and plasma thiocyanate (SCN) concentrations (colorimetric)⁴; plasma lactate and pyruvate (enzymatic); arterial and mixed venous blood oxygen tensions (IL electrode); pH_a , buffer base, hemoglobin concentration, oxygen saturations (IL electrode and CO-Oximeter); plasma sodium and potassium (flame photometers); plasma creatinine (colorimetric); cardiac output (dye-dilution); and mean arterial pressure (strain gauge). Arterial pressures and EKG tracings were continuously displayed.

Control studies included two dogs with bilateral ureteral ligations monitored for 48 hours without SNP administration, and two animals without bilateral ureteral ligations given SNP, 1.0 mg/kg/hr, as in the prior study.

Nitroprusside‡ was administered through a catheter inserted into the superior vena cava via an external jugular vein, which was not used for other purposes, and was checked hourly for leakage. The dosage of SNP was maintained by calibrated Harvard syringe pump. SNP solution was protected from light. Two anuric dogs were given SNP, 0.25 mg/kg/hr, six were given 0.5 mg/kg/hr, two received 0.75 mg/kg/hr, seven were given 1.0 mg/kg/hr, and five were given 1.25 mg/kg/hr (table 1).

Necropsies were performed on all animals, specifically to check for completeness of ureteral ligations, to determine that the bladder was empty, and to verify positioning of monitoring lines.

Results were analyzed by the Students *t* test for unpaired data. $P < 0.05$ was considered significant.

Results

Both control animals without ureteral ligations given SNP, 1.0 mg/kg/hr, died within 36 hours, with blood CN values not different from those reported previously.² Evidence of CN toxicity again included metabolic acidosis, increased lactate/pyruvate ratio, and increased mixed venous blood P_{O_2} , as previously reported.² Both control animals with ureteral ligations given no SNP survived 48 hours. Plasma K^+ increased at least two and a half times, and creatinine increased to more than 5 mg/dl in each animal. At 48 hours, although both dogs were still alive, bradycardia was present (table 1).

Anuric dogs given SNP experienced increases in plasma K^+ and creatinine values at rates similar to those of the control anuric animals. They were, however, unexpectedly more resistant to development of cyanide toxicity than were the normal dogs studied previously.² Both anuric dogs given SNP, 0.25 mg/kg/hr, survived 48 hours with increased plasma SCN levels, but without increased blood CN. Four of the six dogs given SNP, 0.5 mg/kg/hr, died prior to 48 hours, but with only minimally increased blood CN of 0.4 $\mu\text{g/ml}$ (lethal blood CN range is 5–7 $\mu\text{g/ml}^2$). Two anuric dogs given SNP 0.75 mg/kg/hr, survived 36 hours, with an average blood CN at death of only 1.0 $\mu\text{g/ml}$. Of the seven anuric dogs given SNP, 1.0 mg/kg/hr, five did not have the expected progressive increase in blood CN, or metabolic evidence of CN toxicity ("Group without toxicity," figs. 1 and 2; table 2). The remaining two did show nearly linear increases in blood CN, to peaks of 6.6 and 10 $\mu\text{g/ml}$, with deaths at 27 and 44 hours, respectively ("group with toxicity," figs. 1 and 2; table 2). Mean values from all seven animals were used for comparisons with the previously studied normal dogs given a similar SNP dose (figs. 3 and 4; table 3). At and after 32 hours of SNP infusion, average blood CN values were significantly lower in the anuric dogs than in the normal dogs (fig. 3). Plasma thiocyanate levels were significantly higher at and after 24 hours in the anuric dogs than in the normal dogs (fig. 4). Five anuric dogs were given SNP 1.25 mg/kg/hr. Blood CN values increased rapidly and nearly linearly in all, with an average time to death of 21 hours. Blood CN values at death averaged 11.4 $\mu\text{g/ml}$, ranging from 8.9 to 15.0 $\mu\text{g/ml}$. Metabolic

‡ Sodium nitroprusside dihydrate, Roche Laboratories, Nutley, N. J.

TABLE 1. Anuric Dogs, Chronic

SNP Dosage (mg/kg/hr)	Number of Dogs	Time to Death (Hours)	Blood CN* ($\mu\text{g/ml}$)		Plasma SCN ($\mu\text{g/ml}$)		Plasma K ⁺ (mEq/l)		Plasma Creatinine (mg/dl)		pH_a		Buffer Base (mEq/l)	
			Control	Final	Control	Final	Control	Final	Control	Final	Control	Final	Control	Final
0	2	48 \pm 0	.01 \pm 0	.1 \pm .1	.5 \pm .1	0.6 \pm .2	3.6 \pm .1	8.0 \pm .3	0.9 \pm .1	5.7 \pm .1	7.35 \pm .01	7.39 \pm .03	44 \pm 1	43 \pm 2
0.25	2	48 \pm 0	.01 \pm .01	.02 \pm .02	.7 \pm .1	17.0 \pm .2	3.4 \pm .3	7.2 \pm .7	1.1 \pm .2	6.5 \pm .7	7.37 \pm .01	7.33 \pm .02	41 \pm 0	40 \pm 1
0.50	6	41 \pm 3	.04 \pm .02	0.4 \pm .1	.7 \pm .1	38 \pm 5	3.0 \pm .2	7.8 \pm .6	0.9 \pm .1	6.4 \pm .6	7.34 \pm .03	7.30 \pm .01	41 \pm 1	37 \pm 2
0.75	2	38 \pm 1	.02 \pm .02	1.0 \pm .7	.5 \pm 0	55 \pm 2	3.9 \pm .4	7.1 \pm 1.7	0.9 \pm .3	6.3 \pm .4	7.40 \pm .04	7.37 \pm .07	44 \pm 2	38 \pm 2
1.00	7	36 \pm 3	.03 \pm .02	4.0 \pm 1.2	.9 \pm .1	59 \pm 6	3.2 \pm .2	5.9 \pm .6	0.9 \pm .1	5.7 \pm .5	7.33 \pm .01	7.36 \pm .05	40 \pm 0	39 \pm 2
1.25	5	21 \pm 3	.13 \pm .07	11.7 \pm 1.0	.5 \pm .2	41 \pm 5	3.0 \pm .1	6.6 \pm .2	0.6 \pm .1	4.6 \pm .3	7.33 \pm .03	7.23 \pm .08	40 \pm 1	34 \pm 3

* Final hemodynamic and blood-gas data are last regular determinations before death. Other samples for chemical analyses were obtained at death.

† Mean \pm SEM.

evidence of CN toxicity was reflected by a threefold increase in average lactate/pyruvate ratio at 16 hours, three hours before the first animal died. Metabolic acidosis also developed at least four hours prior to death in all but one of these animals, as well as in the two (of seven) animals given SNP, 1.0 mg/kg/hr, that did have linear increases in CN (group with toxicity). Comparative blood CN and plasma SCN values for anuric dogs given SNP doses of 0.5, 1.0, and 1.25 mg/kg/hr are presented in figures 5 and 6 and table 1. At the last regular determinations before death, whole-blood CN values averaged $0.4 \pm .02$, 4.0 ± 1.2 , and $11.7 \pm 1.0 \mu\text{g/ml}$ in the groups given SNP, 0.5, 1.0, and 1.25 $\mu\text{g/kg/min}$, respectively. Similarly, plasma SCN values averaged 38 ± 5 , 59 ± 6 , and $41 \pm 5 \mu\text{g/ml}$ for the same groups, respectively.

Cardiac output and mean arterial pressure values were well maintained in all groups of anuric dogs until one or two hours prior to death (table 1). Pul-

monary-capillary wedge pressures were stable, without evidence of fluid overload, right or left ventricular failure, or pulmonary edema in any animal. The anuric animals showed the expected steady increases in plasma K⁺, with this value increasing to at least two times control at death except in the animals experiencing the linear increases in blood CN, wherein cyanide toxicity led to death in less than 22 hours. Plasma creatinine values increased similarly, to at least four times control at death (table 1).

Comparisons between normal dogs previously studied² and anuric dogs indicated that, at death, blood CN averaged $4.0 \pm 1.2 \mu\text{g/ml}$ in the seven anuric dogs given SNP, 1.0 mg/kg/hr, whereas the eight normal dogs previously reported had an average of $9.0 \pm 1.4 \mu\text{g CN/ml}$ whole blood ($P < .01$). Plasma SCN values were significantly higher in the anuric dogs, 59 ± 6 vs. $32 \pm 4 \mu\text{g/ml}$ ($P < .05$), at SNP, 1.0 mg/kg/hr, compared with the normal dogs previously studied (table 3). The seven anuric dogs given SNP, 1.0 mg/kg/hr, can be divided into groups with and without tox-

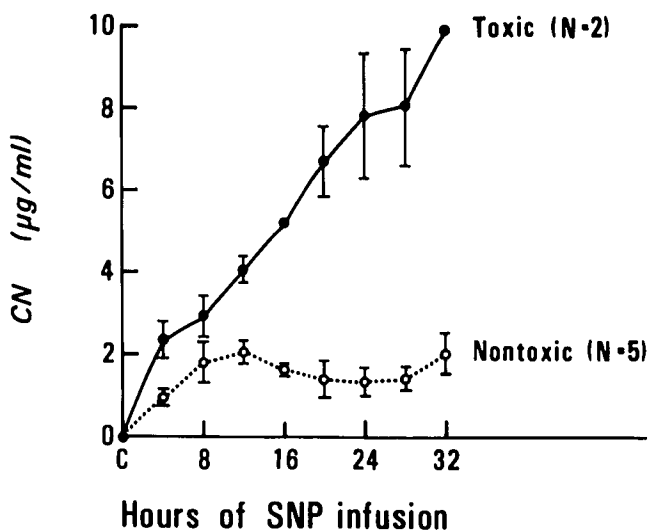


FIG. 1. Blood cyanide (CN) values in seven anuric dogs given SNP, 1.0 mg/kg/hr. Two animals (toxicity group) developed linear increases in blood CN and metabolic evidence of CN toxicity. The other five (group without toxicity) did not. See table 2. This dose apparently was at or near the animal's CN detoxification capacity.

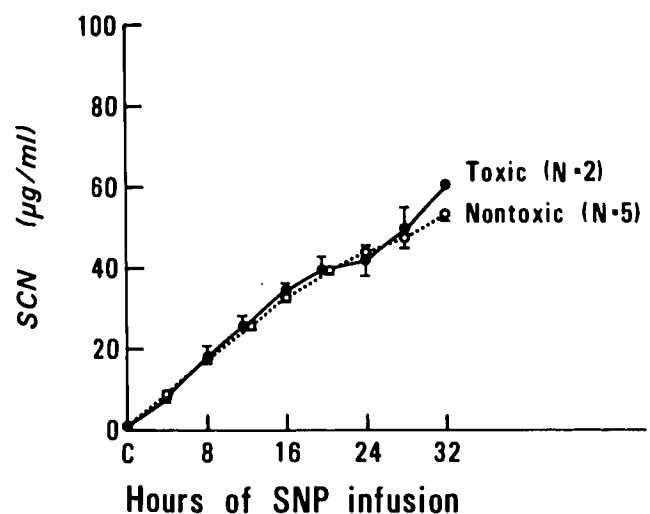


FIG. 2. Plasma thiocyanate (SCN) values in seven anuric dogs given SNP, 1.0 mg/kg/hr. The groups with and without toxicity accumulated SCN at nearly identical rates, despite the fact that CN toxicity developed in the former. (fig. 1, table 2).

SNP Data,* Control vs. Final†

Lactate/Pyruvate Ratio			Mean Arterial Pressure (torr)			Heart Rate (beats/min)			Whole-body \dot{V}_{O_2} (ml/min/m ²)			Cardiac Index (ml/min/m ²)		
Control	Final	Per Cent Change	Control	Final	Per Cent Change	Control	Final	Per Cent Change	Control	Final	Per Cent Change	Control	Final	Per Cent Change
10 ± 2	9 ± 1	-10	93 ± 5	91 ± 8	+1	168 ± 20	94 ± 14	-44	6.8 ± .2	6.7 ± .4	-2	84 ± 15	90 ± 8	+7
11 ± 1	8 ± 3	-27	84 ± 2	88 ± 11	+5	150 ± 30	100 ± 40	-33	6.1 ± .2	6.6 ± .5	+8	81 ± 16	100 ± 2	+23
11 ± 3	12 ± 1	+9	136 ± 8	76 ± 11	-44	175 ± 10	105 ± 15	-40	6.6 ± .9	5.9 ± .04	-11	125 ± 18	102 ± 7	-18
11 ± 2	20 ± 10	+82	127 ± 8	53 ± 1	-58	170 ± 30	140 ± 20	-18	5.0 ± .1	4.6 ± .4	-8	140 ± 10	78 ± 1	-44
10 ± 1	21 ± 4	+100	127 ± 5	46 ± 22	-64	143 ± 11	80 ± 35	-44	6.4 ± .7	3.8 ± 1.4	-41	159 ± 20	80 ± 52	-50
11 ± 1	36 ± 3	+227	124 ± 6	21 ± 3	-83	191 ± 18	191 ± 18	-35	5.0 ± .6	4.3 ± 3.0	-14	124 ± 28	64 ± 46	-48

icity (fig. 1). At death, blood CN values averaged 8.3 ± 1.7 vs. $2.3 \pm .5$ $\mu\text{g/ml}$ in the groups with and without toxicity, respectively. Plasma SCN values, however, were nearly identical, averaging 63 ± 17 and 58 ± 7 $\mu\text{g/ml}$ in the groups with and without toxicity, respectively, indicating that SNP, 1.0 mg/kg/hr, was at or near the anuric dogs' upper limit of CN detoxification ability (table 2).

Discussion

Low-cardiac-output states, with increased peripheral vascular resistance, are often treated with vasodilator drugs, such as SNP. Oliguria or anuria is a frequent accompanying problem. Perhaps due to increased circulating catecholamine levels, or because enough renal blood flow is present to preserve the renin-angiotensin-mediated "defenses" against vasodilators, the dosage of SNP necessary to accomplish the desired hemodynamic effects may be relatively large. The bilateral ureteral ligation model was chosen for this

study because with intact renal blood supply and presumed intact renin-angiotension mechanisms, the animals tolerated doses of SNP large enough to test the hypothesis that CN toxicity might be more likely when renal excretory function was blocked.

The hemodynamic, ureteral pressure, and renal vascular resistance responses to both unilateral and bilateral ureteral ligations have been extensively investigated.⁵⁻¹² These studies indicate that although proximal ureteral pressure increases progressively, the increase is modest and does not result in a decrease in renal blood flow sufficient to lead to renal ischemia. The data of Moody *et al.*,⁵ obtained after 24 hours of bilateral ureteral obstruction in dogs, indicate that total renal blood flow was decreased to 38 per cent of control, while ureteral pressure increased from 31 torr 15 min after ligation to 41 torr at 24 hours. Because SNP is a renal vasodilator,¹³ the decrease in renal blood flow might be retarded to some extent. No study of this point is extant. Systemic arterial pressure

TABLE 2. Anuric Dogs Given SNP, 1.0 mg/kg/hr, with and without Toxicity, Data* at Death

	Number of Dogs	Time to Death (Hours)	Blood CN ($\mu\text{g/ml}$)	Plasma SCN ($\mu\text{g/ml}$)	pH _a	Plasma K ⁺ (mEq/l)	Buffer Base (mEq/l)	Lactate/Pyruvate Ratio
Without toxicity	5	37 ± 4	2.3 ± .5	58 ± 7	7.44 ± .02	6.4 ± .7	41.8 ± 2.0	16 ± 5
With toxicity	2	36 ± 8	8.3 ± 1.7	63 ± 18	7.20 ± .03	4.8 ± 2.0	34.0 ± 2.0	25 ± 1

* Mean ± SEM.

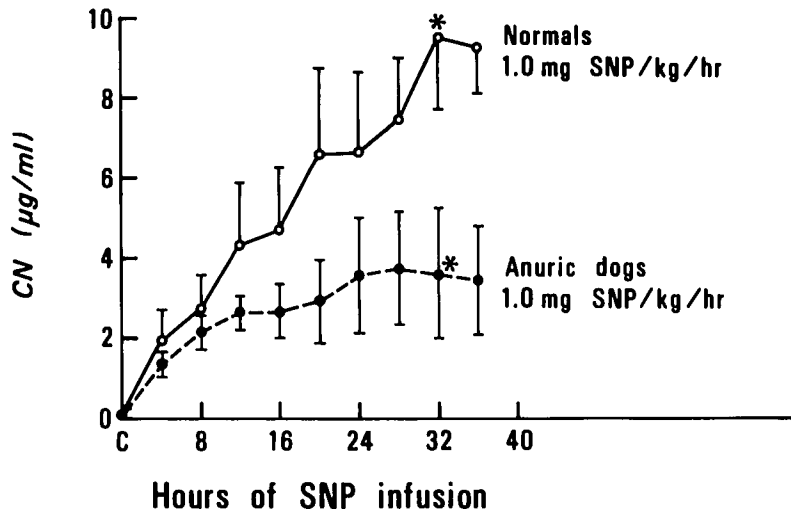
TABLE 3. Data* at Death, Anuric vs. Normal† Dogs

	Number of Dogs	Time to Death (Hours)	Blood CN ($\mu\text{g/ml}$)	Plasma SCN ($\mu\text{g/ml}$)	pH _a	Buffer Base (Per Cent Decrease from Control)	Lactate/Pyruvate Ratio
Anuric 1.0 mg SNP/kg/hr	7	36 ± 3	4.0 ± 1.2‡	59 ± 6‡	7.36 ± .05	2‡	21‡
Normal† 0.75 mg SNP/kg/hr (3 dogs) 1.0 mg SNP/kg/hr (5 dogs)	8	37 ± 2	9.0 ± 1.4	32 ± 4	7.27 ± .05	17	41

* Mean ± SEM.

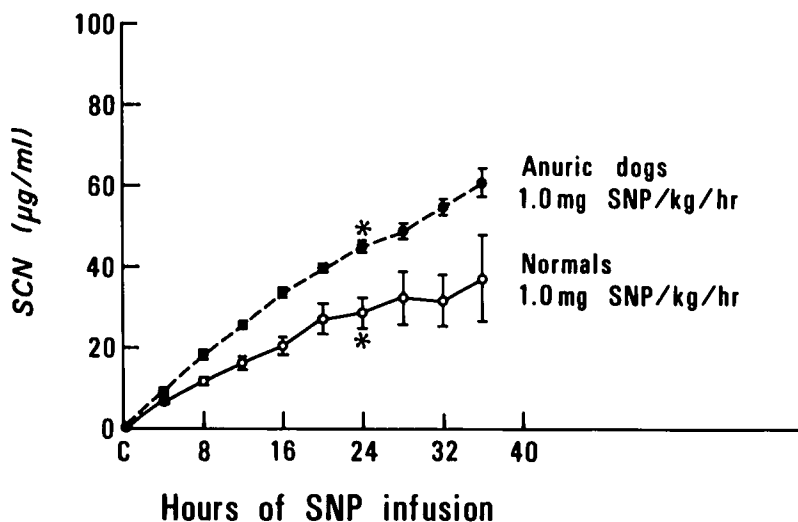
† Data from Michenfelder JD, Tinker JH: ANESTHESIOLOGY 47:441-448, 1977.

‡ Significant difference ($P < 0.05$ or less) between anuric and normal groups (Student *t* test for unpaired data).



† Data from Michenfelder, J.D. and Tinker, J.H.; ANESTHESIOLOGY
47: 441-448, 1977.
* $P < .05$

FIG. 3. Blood CN values in anuric dogs given SNP, 1.0 mg/kg/hr, compared with previously reported values for normal dogs given the same dose. Blood CN values were significantly lower at and beyond 32 hours in the anuric animals.



† Data from Michenfelder, J.D. and Tinker, J.H.; ANESTHESIOLOGY
47: 441-448, 1977.
* $P < .05$

FIG. 4. Plasma SCN values in anuric dogs given SNP, 1.0 mg/kg/hr, compared with previously reported values for normal dogs given the same dose. Plasma SCN values were significantly higher at and beyond 24 hours in the anuric animals.

is not significantly altered by unilateral or bilateral ureteral obstruction.⁵ The ureterally obstructed kidney responds by increasing renin release, although the observed gradually decreasing renal blood flow is not altered by administration of angiotensin II antagonist.¹⁴ Nephrectomized dogs (pilot studies only) tolerated a dose of SNP that was too small to obtain CN release sufficient to produce toxicity. The animals with bilateral ureteral ligations initially showed the usual canine tolerance to SNP, enabling CN toxicity studies to be carried out.

In the normal dogs previously studied,² all animals given SNP, 0.5 mg/kg/hr, survived the 48-hour period

without evidence of CN toxicity, whereas death due to CN toxicity occurred in 30–36 hours in the animals given 0.75 and 1.0 mg/kg/hr. In the animals not experiencing toxicity, blood CN values increased early, but steadied at values less than 2 µg/ml. The anuric animals studied herein given no SNP or 0.25 mg/kg/hr survived 48 hours without increased CN levels, but with a doubling or tripling of plasma K^+ values, and with marked bradycardia during the last few hours. Of the six dogs given 0.5 mg/kg, only two survived the entire 48 hours. Blood cyanide values above 2.0 µg/ml were not seen in any anuric animal given this dose, nor did metabolic acidosis develop

FIG. 5. Blood CN values in anuric dogs chronically given SNP, 0.5, 1.0, and 1.25 mg/kg/hr. Animals both with and without toxicity are included in the 1.0 mg/kg/hr dosage group.

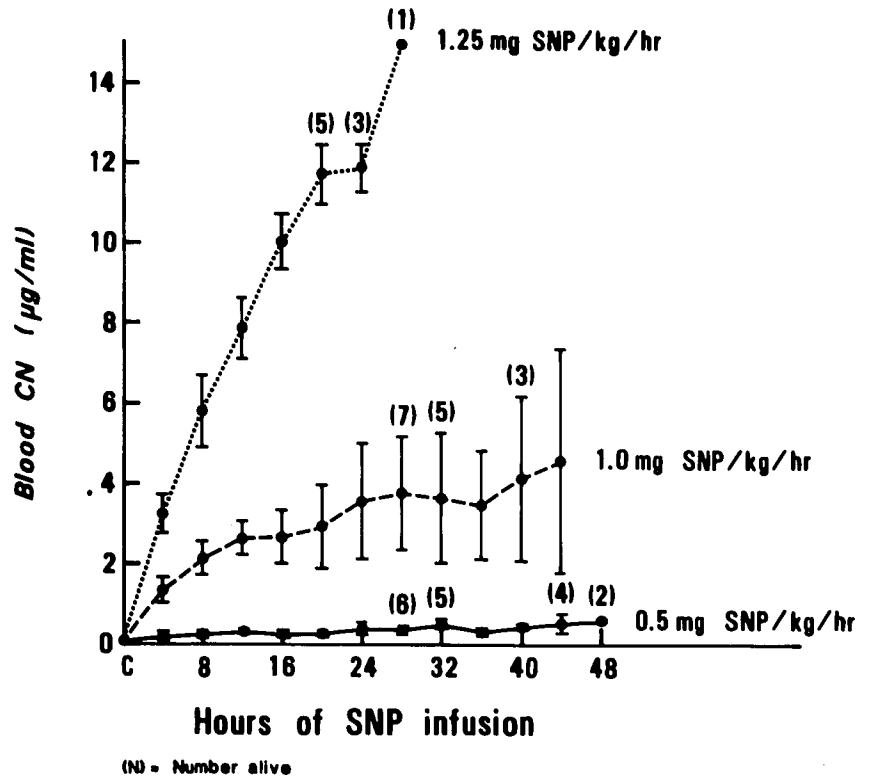
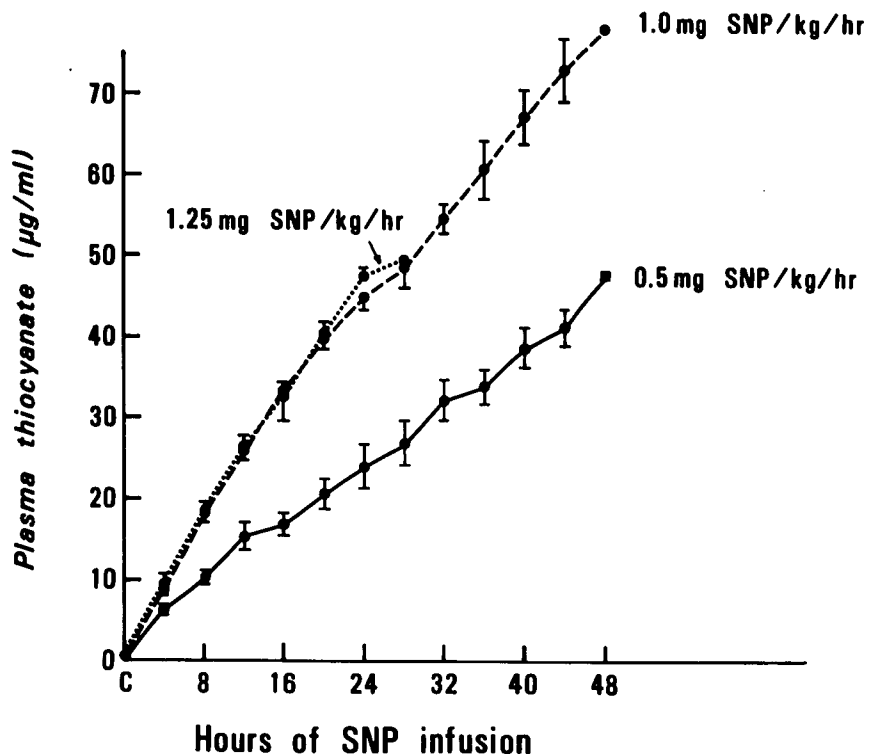


FIG. 6. Plasma SCN values in anuric dogs chronically given SNP, 0.5, 1.0, and 1.25 mg/kg/hr. Rates of accumulation of SCN are nearly identical at 1.0 and 1.25 mg/kg/hr, indicating maximum utilization of sulfur donor. CN toxicity developed in only two of seven dogs given 1.0 mg/kg/hr, but in all animals given 1.25 mg/kg/hr, indicating that plasma SCN measurements are not useful monitors for SNP-induced CN toxicity.



until bradycardia and severe hypotension occurred. Mixed venous blood P_{O_2} values did not increase. Neither of the two dogs given 0.75 mg/kg/hr and none of the seven dogs given 1.0 mg/kg/hr survived the full

48 hours. Still, in only two of the dogs given 1.0 mg/kg/hr did a progressive increase in blood CN develop, with early metabolic acidosis and increased mixed venous blood P_{O_2} values. Thus, we consider that the other

animals died of the combination of excretory failure, with progressive hyperkalemia and bradycardia, plus the hypotension caused by the increasing dosages of SNP itself. In the two animals given 1.0 mg/kg/hr wherein the CN detoxification mechanism had presumably been overloaded, near-linear increases in blood CN, early metabolic acidosis, and increased mixed venous blood P_{O_2} values all occurred. All five dogs given the next SNP increment, 1.25 mg/kg/hr, showed near-linear increases in CN values and metabolic evidence of CN toxicity. Therefore, although the anuric dogs did not show better survivability, they demonstrated increased ability to detoxify CN when compared with the normal dogs studied previously.²

The rates of accumulation of plasma SCN are of interest. At 36 hours, SCN levels were significantly higher in the anuric animals than in the normal dogs at the 0.5 mg/kg/hr dose; SCN levels were significantly higher at and beyond 24 hours in the anuric dogs given SNP, 1.0 mg/kg/hr, compared with the normal dogs studied previously. This plus the lower CN levels in the anuric animals provides the basis for our conclusion that the observed increased resistance to CN accumulation was due to increased production of SCN, due in turn to increased availability of sulfur donor, probably thiosulfate. The normal animals probably excreted some SCN during the first 24–36 hours, but this compound is only slowly eliminated in the urine, distributing itself in extracellular fluids in a manner similar to that of the halogens, and becoming incorporated into the total halogen pool with respect to excretion.¹⁵ SCN is, in fact, a normal constituent of extracellular fluid.¹⁶ Thus, at 24 and 36 hours, at 1.0 mg/kg/hr, the average cyanide level in the anuric dogs was significantly lower and the average thiocyanate level was significantly higher, compared with the normal dogs studied previously.²

Also of interest regarding SCN accumulation was the fact that, in the anuric dogs, the rates of SCN accumulation were nearly identical at 1.0 and 1.25 mg/kg/hr (fig. 2). That two of the seven anuric dogs given 1.0 mg/kg/hr had near-linear CN increases while the other five in this group did not indicated that this dose of SNP released sufficient CN to approach the maximum CN detoxification capability, given only an endogenous sulfur donor supply. At the next increment, 1.25 mg/kg/hr, SCN accumulated at the same rate as at the previous SNP dose, indicating a maximum rate of SCN production. The near-linear blood CN accumulation at this dose indicated that the upper limit of detoxification had been exceeded by the rate of CN release.

The above explanation for the observed increased resistance to CN toxicity, namely increased availability of sulfur donor, depends upon the existence of a pathway whereby this could be accomplished. The principal sulfur donor, thiosulfate, formerly thought not to be a normal component of urine,¹⁷ has recently been found in small quantities in human and dog urine by Ivankovich and his colleagues,[§] and thus would be expected to accumulate slowly in excretory failure. Other excreted compounds can also be converted into thiosulfate. Breakdown of the sulfur-containing amino acid cysteine results in β -mercaptopyruvic acid (also called β -thiolpyruvic acid). Thiosulfate can be formed from a reaction between β -mercaptopyruvate and sulfite ion. Normally, most sulfite is oxidized by hepatic sulfite oxidase to sulfate ion and excreted. There is human evidence, however, that sulfite oxidase deficiency can result in the accumulation and excretion of large amounts of thiosulfate.¹⁸ This indicates interchangeability between the pathways leading to the production of sulfate (via sulfite) and thiosulfate (via sulfite + β -mercaptopyruvate). In the anuric dogs, thiosulfate was being "consumed" by conversion into thiocyanate, whereas sulfate excretion was blocked. While we have no direct evidence, the decreased blood CN levels and increased plasma SCN levels in these anuric animals compared with normal dogs given the same SNP dosage is indirect evidence of increased thiosulfate availability.

A possible alternative explanation for the observed increased tolerance to CN in anuric dogs might be that obliteration of renal excretion somehow decreased breakdown of SNP into CN. This breakdown probably occurs via a nonenzymatic reaction with oxyhemoglobin,¹⁹ which is in gross excess and would therefore be unaffected in the anuric state. Also, the rate of accumulation of SCN was significantly higher in the anuric dogs, indicating that CN release was probably proceeding normally. In addition, the near-linear increases in blood CN in the two toxic dogs given 1.0 mg/kg/hr, but not in the other five given this dose, with similar SCN accumulations in both groups, is evidence that CN release from SNP was proceeding as usual, and that whether or not CN accumulation occurred depended upon adequacy of detoxification (*i.e.*, availability of sulfur donor).

The two control animals not subjected to bilateral ureteral ligations given 1.0 mg/kg/hr showed near-linear CN accumulation and death with metabolic acidosis and increased mixed venous blood P_{O_2} values,

§ Ivankovich AD, Abraham Lincoln School of Medicine, personal communication.

similar to those of normal dogs studied previously.² This negates the possibility that, because the two studies were done 18 months apart, dietary or other differences might have altered SNP breakdown or CN detoxification in the dogs in the present study.

The results of this study indicate also that accumulation of SCN does not inhibit release of CN from SNP. This was demonstrated by the finding that while anuric dogs given SNP, 1.25 mg/kg/hr, produced SCN at a rate not greater than that in the dogs given 1.0 mg/kg/hr, they accumulated CN at a greater rate.

The present study also confirms our previous conclusion² that plasma SCN levels do not accurately reflect blood CN levels and are therefore not useful as a monitor for CN toxicity in patients receiving SNP. Rather, plasma SCN levels reflect cyanide release coupled with sulfur donor availability plus distribution and excretion of SCN.

The increased resistance to SNP-induced CN toxicity reported herein is not of sufficient magnitude to suggest that the maximum chronic SNP dosage previously recommended (0.5 mg/kg/hr; 8 µg/kg/min) can be increased in oliguric or anuric patients. However, based on this study, should an oliguric or anuric patient need a relatively large dose of SNP to obtain a desired hemodynamic effect, the maximum permissible SNP dosage need not be decreased because of concern over enhancement of CN toxicity by excretory failure. We conclude that: 1) cyanide toxicity occurred at higher chronic doses of SNP in anuric dogs than in normal dogs previously studied; 2) this is probably accounted for by increased availability of endogenous sulfur donor due to excretory failure; 3) based on these canine studies, arbitrary decreases in SNP dosage in anuric or oliguric patients because of the risk of CN toxicity would not seem likely to be necessary.

References

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