

Cyanide Toxicity and Thiosulfate Protection during Chronic Administration of Sodium Nitroprusside in the Dog:

Correlation with a Human Case

John D. Michenfelder, M.D.* and John H. Tinker, M.D.†

Guidelines have been established for the safe maximum dosage of sodium nitroprusside (SNP) when administered over a brief period (1-3 hours). No such guidelines have been established for prolonged administration of the drug. Accordingly, dogs were given continuous infusions of various concentrations of sodium nitroprusside (SNP) and monitored for 48 hours or until death. Dogs given 0.5 mg/kg/hr did not have cyanide toxicity, achieving and maintaining blood cyanide levels of about 2 μ g/ml. In animals given SNP, 0.75-1 mg/kg/hr, blood cyanide levels increased progressively to above 7 μ g/ml and death occurred after 30-38 hours. Cyanide toxicity in these animals was evidenced early by progressive metabolic acidosis, increased mixed venous blood oxygen tension, and decreased oxygen consumption. Dogs given SNP, 1 mg/kg/hr, plus thiosulfate, 6 mg/kg/hr, survived 48 hours without evidence of cyanide toxicity, and blood cyanide levels remained low (about 2 μ g/ml). Serum thiocyanate levels did not correlate with development of cyanide toxicity. The results of this study are correlated with the events preceding a human fatality, which occurred after the requirement for SNP increased to between 0.5 and 1 mg/kg/hr for 24 hours, following prolonged infusion at a much lower dose. The authors conclude that a) the dog is an acceptable model for study of SNP-related cyanide toxicity, b) chronic SNP administration should not exceed 0.5 mg/kg/hr, c) simultaneous thiosulfate administration affords protection against SNP-related cyanide toxicity, d) serum thiocyanate levels do not predict or reflect cyanide toxicity, and e) development of metabolic acidosis and increased mixed venous blood oxygen tension best reflect development of cyanide toxicity. (Key words: Anesthetic techniques, hypotension, induced, nitroprusside; Blood pressure, hypotension; Toxicity, cyanide; Toxicity, nitroprusside; Toxicity, thiocyanate; Pharmacology, thiosulfate; Pharmacology, nitroprusside.)

THE POTENTIAL for cyanide (CN) toxicity during sodium nitroprusside (SNP) administration is established.^{1,2} Acute animal studies and individual case reports of toxicity have resulted in recommendations regarding the maximum safe dose of nitroprusside that can be administered acutely (that is, in a period of one to several hours). Recommended maximum acute dosages range from 1.5 to 3.5 mg/kg.³⁻⁵ Recent human⁴ and canine⁵ studies suggest that early toxicity can be recognized at doses exceeding 1.5 mg/kg.

* Professor of Anesthesiology.

† Assistant Professor of Anesthesiology.

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Medical School, Rochester, Minnesota 55901. Accepted for publication June 10, 1977. Supported in part by Research Grants NS-7507 and GM-21729 from the National Institutes of Health, Public Health Service.

Address reprint requests to Dr. Michenfelder.

That similar dosage recommendations were derived from different laboratories in studies of both dog and man suggests that the dog is an acceptable model for investigation of nitroprusside toxicity due to cyanide release.

Nitroprusside is used acutely for the intraoperative induction of controlled hypotension and chronically for the control of hypertension, decrease of afterload, and the treatment of vascular spasm. To our knowledge, no investigation has attempted to establish the maximum safe dosage of nitroprusside when administered chronically. Recently we encountered a human fatality, presumed due to cyanide toxicity during chronic nitroprusside therapy. Apparent toxicity occurred 24 hours following an increase in dose requirement to 0.5-1 mg/kg/hr, after prolonged infusion at a much lower dose.

The present investigation was designed to determine in dogs the maximum dose of nitroprusside that can be administered during a 48-hour period without the development of cyanide toxicity. In addition, laboratory tests that might permit early recognition of cyanide toxicity and the efficacy of thiosulfate administration for protection against cyanide toxicity were evaluated.

Materials and Methods

Twenty-seven fasting unmedicated mongrel dogs weighing 9-11 kg were studied in groups of two or three in a simulated "intensive care" situation while breathing nitrous oxide, 70 per cent, and oxygen (humidified). Endotracheal intubation was accomplished after muscle paralysis with succinylcholine, 40 mg, intravenously. Thereafter, paralysis was maintained with pancuronium, 0.1 mg/kg, iv, approximately every two hours. Ventilation was controlled with a Harvard pump to maintain an arterial blood tension of carbon dioxide of 35 ± 1 torr (mean \pm SE). In every dog, a femoral artery and vein were cannulated for monitoring mean arterial pressure (MAP), blood sampling, and drug and fluid administration. A forelimb vein was cannulated for continuous administration of nitroprusside using a Harvard syringe pump. In 12 of the animals a balloon-tipped catheter was inserted into the pul-

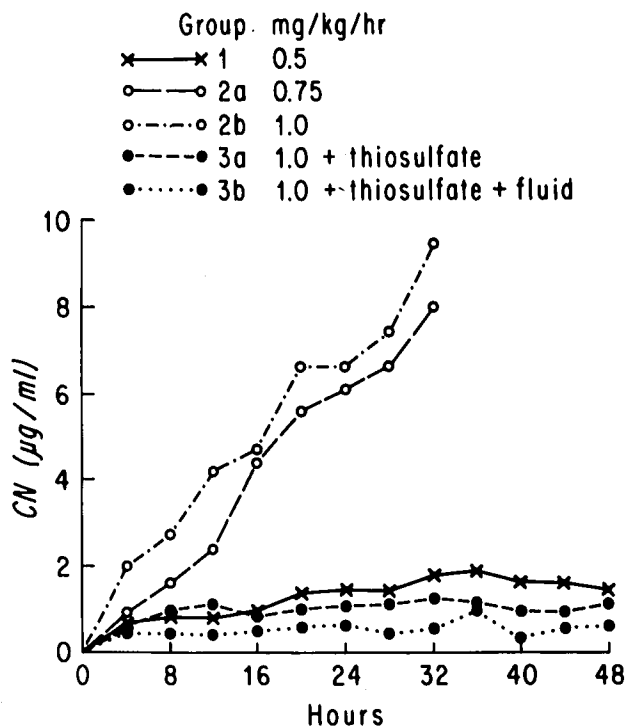


FIG. 1. Whole-blood cyanide levels during continuous infusion of sodium nitroprusside in five groups of dogs. In dogs not given thiosulfate and at a dose of either 0.75 or 1.0 mg/kg/hr (Group 2a, b) CN increased progressively with time. Values in these animals after 32 hours are not shown in this and subsequent figures because of variability in times of death (between 30 and 38 hours). At a dose of 0.5 mg/kg/hr (Group 1) or in dogs given 1.0 mg/kg/hr with thiosulfate (Group 3a, b) an initial increase in CN occurs, but thereafter CN is maintained for 48 hours at a relatively low level.

monary artery via a jugular vein for obtaining mixed venous blood samples and cardiac output determinations. Esophageal temperature was monitored by thermistor. Urinary output was recorded hourly (urethral catheter). Electroencephalogram (two-lead bifrontal) and electrocardiogram (lead II) records were obtained hourly.

Control measurements included whole-blood cyanide (CN) and serum thiocyanate (SCN) concentrations (colorimetric),⁶ lactate and pyruvate concentrations (enzymatic); arterial blood oxygen and carbon dioxide tensions,[‡] pH, and buffer base (BB⁺), hemoglobin (Hb) concentration, and O₂ saturation[§]; serum sodium and potassium concentrations (flame photometer); cardiac output (dye dilution); MAP (strain gauge). Blood O₂ contents (arterial and mixed venous) were calculated from dissolved O₂ (P_{O₂}) and oxyhemoglobin concentrations. Whole-body oxygen

‡ IL electrodes.

§ IL Co-Oximeter.

consumption (\dot{V}_{O_2}) was calculated from cardiac output (\dot{Q}) and arterial-mixed venous blood O₂ content difference [$C(a-\bar{v})_{O_2}$] using the Fick relationship. After initiation of the nitroprusside infusion, these measurements were repeated every four hours. MAP was continuously monitored with an oscilloscope.

Care and maintenance of the dogs included the following: body temperature was maintained at 37.5 ± 0.2 C with heat lamps or ice bags as needed; penicillin G, 600,000 units, and bicillin, 200,000 units, were given intramuscularly after induction of anesthesia; fluid therapy consisted of 5 per cent dextrose in 0.45 per cent saline solution, 2.5 ml/kg/hr; the lungs were hyperinflated hourly and the trachea suctioned as needed; inspired P_{O₂} was adjusted to maintain Pa_{O₂} above 100 torr; cross-matched blood was transfused if the hemoglobin value decreased to 11.0 g/dl. The animals were continuously attended.

The dogs were divided into five groups determined by dose of nitroprusside infused (0.5, 0.75, and 1 mg/kg/hr) plus type (if any) of anticyanide therapy administered (thiosulfate with or without extra fluids). These groups are described in table 1. The studies were terminated after 48 hours or by "death," defined as the onset of either a persistent isoelectric EEG (for longer than an hour) or profound shock (MAP < 25 torr). In three additional dogs the following doses of nitroprusside were administered: 1.5 mg/kg/hr, 2 mg/kg/hr, and 2 mg/kg/hr plus thiosulfate, 12 mg/kg/hr. Control studies included two animals in which only thiosulfate, 6 mg/kg/hr, was given for 48 hours and one in which thiocyanate, 1.25 mg/kg/hr, was given for 48 hours.

In all but two dogs, with onset of one of the criteria for death, tissue samples were rapidly obtained from skeletal muscle, liver, kidney, myocardium, and brain for determination of cyanide concentrations. In the two animals not so sampled, the nitroprusside infusion was discontinued and blood levels of CN and SCN were followed for ten hours. Dogs given 0.5 mg/kg/hr nitroprusside were killed by intravenous injection of potassium after 48 hours, and tissue samples taken as described above. Dogs

TABLE 1. Experimental Protocol

Group	Number of Dogs	Dose of Nitroprusside (mg/kg/hr)	Dose of Thiosulfate (mg/kg/hr)	Fluid Regimen* (ml/kg/hr)
1	4	0.5	None	2.5
2a	3	0.75	None	2.5
2b	5	1.0	None	2.5
3a	5	1.0	6.0	2.5
3b	4	1.0	6.0	5.0

* 5 per cent dextrose in 0.45 per cent saline solution.

given thiosulfate that survived 48 hours were permitted to recover and observed. The two animals given thiosulfate only and one given thiocyanate only were also permitted to recover.

Results

Cyanide toxicity was observed in those dogs given either 0.75 or 1 mg/kg/hr sodium nitroprusside without simultaneous thiosulfate administration (Groups 2a, b). Blood CN levels in these dogs increased in an approximately linear fashion from the beginning of the nitroprusside infusion (fig. 1). The rate and magnitude of increase were somewhat greater in dogs given 1 mg/kg/hr. The earliest death occurred at 30 hours; all of these dogs (Groups 2a, b) succumbed by 38 hours. Death occurred at whole-blood CN levels between 7 and 10 $\mu\text{g/ml}$. In dogs given 0.5 mg/kg/hr nitroprusside with no anticyanide therapy (Group 1), or 1 mg/kg/hr with thiosulfate (Groups 3a, b), blood CN levels increased rapidly at first to approximately 1 $\mu\text{g/ml}$, but remained below 2 $\mu\text{g/ml}$ throughout the 48-hour period (fig. 1). Metabolic evidence of CN toxicity was not observed in these dogs. However, urinary output approximately doubled in the animals given thiosulfate, and two dogs not given extra fluids (Group 3a) died prior to the end of the 48-hour period (at 40 and 47 hours), apparently from hypovolemic shock. Of the remaining seven thiosulfate-treated dogs (Groups 3a, b), all but one recovered and appeared normal. This dog (not given extra fluids) survived 48 hours but ultimately died, again in apparent hypovolemic shock. Serum SCN levels (fig. 2) increased to the highest concentrations in those dogs given thiosulfate (Groups 3a, b), and presumably account for the increases in urinary output. Serum SCN levels were lowest in dogs given 0.5 mg/kg/hr nitroprusside (Group 1). In dogs given 0.75 and 1 mg/kg/hr without thiosulfate treatment (Groups 2a, b), the rates and magnitudes of increases in serum SCN were similar, and at death SCN was less than 50 $\mu\text{g/ml}$ (5 mg/dl).

Mean arterial pressures decreased abruptly 20–40 per cent in all dogs after initiation of the nitroprusside infusion, but thereafter were well maintained without the need for supportive measures. MAP remained above 60 torr until terminal toxicity occurred. Cardiac output also decreased initially with the nitroprusside infusion, but thereafter was well maintained for the 48-hour period, or until just prior to death. In four of the eight dogs with CN toxicity "death" was evidenced by a persistent isoelectric EEG, with adequate hemodynamics; in the remaining four, hemodynamic collapse occurred less than an hour after onset of an isoelectric EEG.

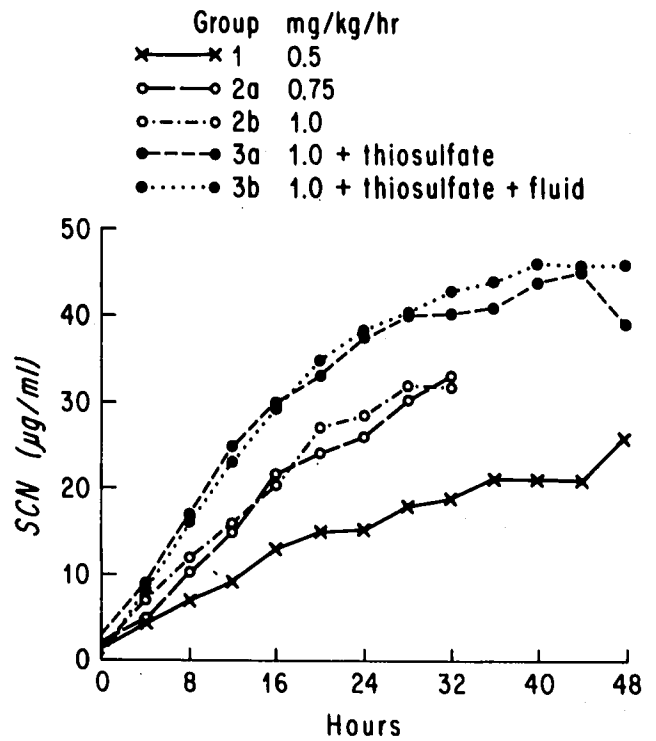


FIG. 2. Serum thiocyanate levels during continuous infusion of sodium nitroprusside in five groups of dogs. The highest SCN levels were produced in those dogs given 1.0 mg/kg/hr with thiosulfate (Group 3a, b). The rate of rise was unaffected by the amount of fluids given and appeared to decrease with time. In dogs given 0.75 or 1.0 mg/kg/hr (Group 2a, b), the rate of rise was similar and approximately linear. In dogs given 0.5 mg/kg/hr (Group 1), SCN levels increased progressively, but at a much slower rate.

Cyanide toxicity was manifested earliest by an increase in mixed venous blood P_{O_2} and by the development of metabolic acidosis (figs. 3–5). These changes became apparent between 20 and 28 hours at whole-blood CN levels of 5–7 $\mu\text{g/ml}$. The patterns of change in these variables were similar in dogs given 0.75 mg/kg/hr and those given 1 mg/kg/hr (Group 2a, b), in agreement with whole-blood CN and serum SCN levels. In dogs given 0.5 mg/kg/hr (Group 1) or 1 mg/kg/hr with thiosulfate (Group 3a, b), $P\bar{v}_{O_2}$ tended to decrease rather than increase, and significant metabolic acidosis did not develop. Judged by serum sodium and potassium levels, significant electrolyte disturbances did not occur in any of the dogs.

For the purpose of statistical comparison and because of similar responses of the above-mentioned variables, dogs given 0.75 and 1 mg/kg/hr (Groups 2a, b) were grouped together, as were the dogs given thiosulfate with or without extra fluids (Group 3a, b). These two groups were then compared with the animals given 0.5 mg/kg/hr (Group 1) (tables 2–4).

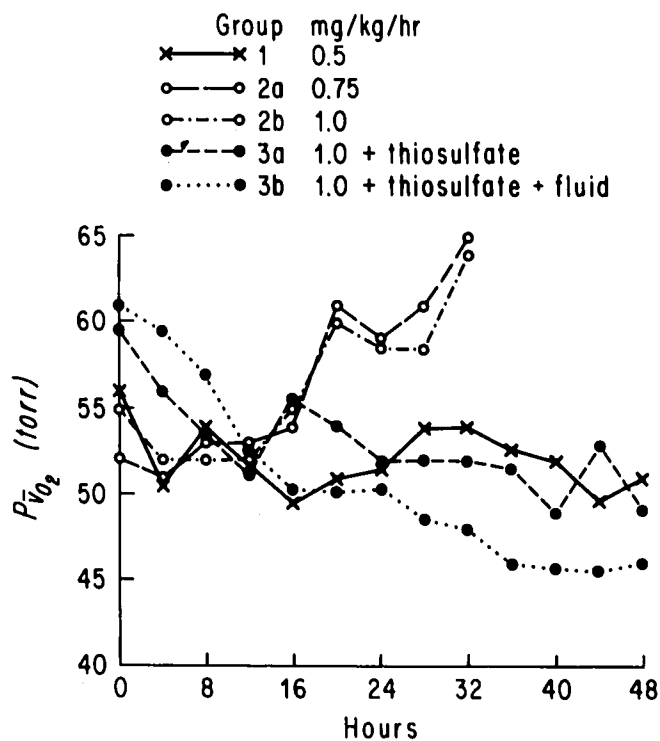


FIG. 3. Mixed venous blood O_2 tension during continuous infusion of sodium nitroprusside in five groups of dogs. After an initial decrease in $P\bar{v}O_2$ (secondary to the decrease in \dot{Q}), $P\bar{v}O_2$ stabilized for about 16 hours. Thereafter, in dogs developing CN toxicity, a progressive increase in $P\bar{v}O_2$ occurred.

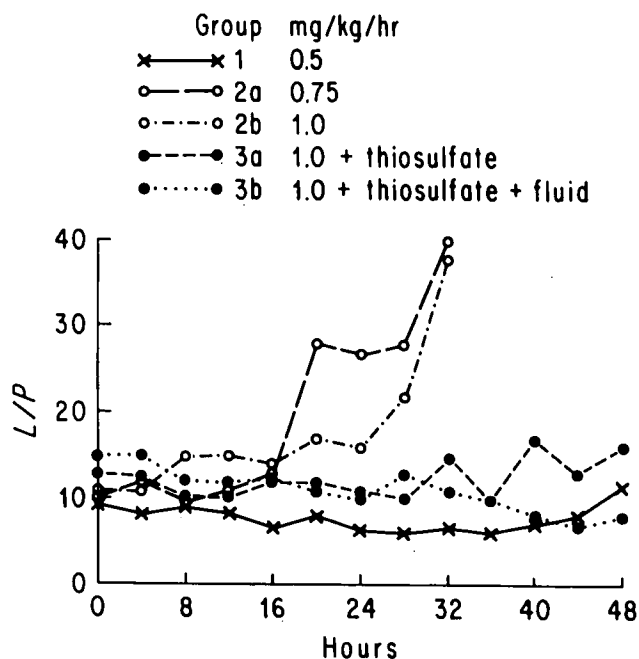


FIG. 4. Lactate-pyruvate ratios during continuous infusion of sodium nitroprusside in five groups of dogs. L/P remained normal for 16 hours, following which a progressive increase was observed only in dogs developing CN toxicity.

Among these three groups there was no meaningful difference in the control values. Values are tabulated at the first four-hour interval and again at 48 hours (or just prior to hemodynamic collapse in the animals in which toxicity developed). The four-hour values presumably reflect nitroprusside effects only, and were similar among the three groups, with reductions in MAP and \dot{Q} from control values. The final values reflect nitroprusside effects plus the effects of CN toxicity and the protective effects of thiosulfate. In the animals in which toxicity developed (table 3), there were significant decreases in pH, buffer base, and $\dot{V}O_2$ values, coupled with significant increases in $P\bar{v}O_2$, lactate, and L/P values. In the thiosulfate-treated animals (table 4), these changes were not observed. There was no significant difference between the final values of dogs given 1 mg/kg/hr with thiosulfate therapy (Group 3a, b) and those (Group 1) given 0.5 mg/kg/hr (table 2) and not treated.

Comparison of tissue CN levels in the three groups (table 5) suggests that the highest levels were generally seen in the animals in which toxicity developed, but the differences are not striking, in part because of the relatively small number of dogs studied and because of considerable variability among individual animals.

In two of the dogs that had persistent isoelectric EEG's without severe hemodynamic depression, the nitroprusside infusion was discontinued. Whole-blood

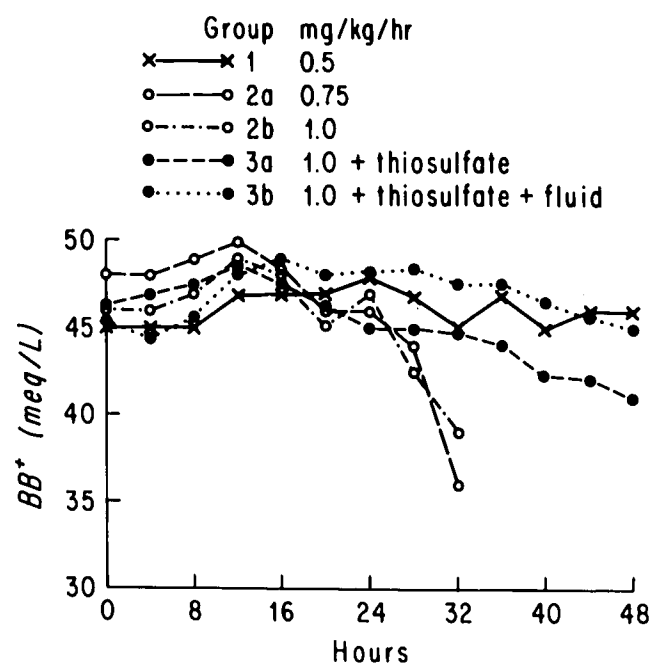


FIG. 5. Buffer base values during continuous infusion of sodium nitroprusside in five groups of dogs. BB^+ remained within a normal range for the initial 24 hours; thereafter, a rapid decline was observed in dogs developing CN toxicity.

TABLE 2. Control, Four-hour, and Final Measurements in Four Dogs Given 0.5 mg/kg/hr Sodium Nitroprusside (Group 1) (Mean ± SE)

	Control	Four Hours	Final
Pa _{o₂} , torr	158 ± 4	148 ± 3	112 ± 18
Pa _{co₂} , torr	33 ± 1	34 ± 1	36 ± 2
pH	7.37 ± 0.03	7.35 ± 0.04	7.39 ± 0.02
BB ⁺ , mEq/l	45 ± 2	45 ± 2	46 ± 2
P _{v̄o₂} , torr*	56 ± 3	50 ± 1	51 ± 3
Lactate, μm/ml	3.05 ± 0.62	1.65 ± 0.35	1.43 ± 0.67
L/P	9 ± 2	9 ± 1	13 ± 3
MAP, torr	137 ± 12	97 ± 12	112 ± 19
HR, beats/min	186 ± 17	211 ± 10	160 ± 17
Q̇, l/min/m ² *	3.54 ± 0.11	2.53 ± 0.10	3.32 ± 0.83
V̇ _{o₂} , ml/min/m ² *	119 ± 23	120 ± 15	104 ± 12
Temperature, C	37.6 ± 0.2	37.4 ± 0.1	37.6 ± 0.2

* Two dogs.

CN and serum SCN levels were followed for ten hours (fig. 6). Whole-blood CN decreased rapidly in an exponential fashion to less than 0.3 μg/ml at ten hours. Serum SCN continued to increase for at least two hours, and then also began to decrease. In the single dogs given 1.5 and 2 mg/kg/hr nitroprusside, toxicity was manifested in a greatly accelerated and dose-related fashion, with death occurring at 19 and 8 hours, respectively. Whole-blood CN levels increased rapidly in these dogs to above 11 μg/ml before death (fig. 7). In the dog given thiosulfate (12 mg/kg/hr) along with 2 mg/kg/hr SNP, protection was provided for 48 hours, with whole-blood CN levels maintained at approximately 2 μg/ml. In the two dogs given thiosulfate only (6 mg/kg/hr) for 48 hours, no toxic effect was apparent; both awakened and appeared normal. In the one dog given thiocyanate only (1.25 mg/kg/hr), SCN levels of 50–60 μg/ml developed; again, no toxicity was apparent in 48 hours.

Discussion

We pursued this investigation partly because of an unexpected fatality in the case of a patient receiving chronic nitroprusside therapy in which the terminal events strongly suggested cyanide toxicity. The relevant events in this case warrant summarizing.

Report of a Case

A 13-year-old, 43-kg boy was admitted with the diagnosis of acute right cerebral infarction, severe hypertension, and coarctation of the aorta. Blood pressure on admission was 210/100 torr. Surgical correction of the coarctation was delayed because of unstable neurologic status, with fluctuating left hemiparesis and varying obtundation. Nitroprusside therapy was initiated to decrease blood pressure to approximately 150 torr systolic and maintain it at that level. Satisfactory blood pressure control was achieved using a dose of approximately 0.07 mg/kg/hr (1.2 μg/kg/min). In the ensuing 24 hours seizure activity, left

TABLE 3. Control, Four-hour, and Final Measurements in Eight Dogs Given 0.75 or 1.0 mg/kg/hr Sodium Nitroprusside (Group 2a, b) (Mean ± SE)

	Control	Four Hours	Final
Pa _{o₂} , torr	131 ± 9	139 ± 6	128 ± 6
Pa _{co₂} , torr	34 ± 1	34 ± 1	34 ± 2
pH	7.41 ± 0.02	7.41 ± 0.02	7.27 ± 0.05†
BB ⁺ , mEq/l	47 ± 1	47 ± 1	38 ± 2†
P _{v̄o₂} , torr*	54 ± 2	52 ± 3	64 ± 1†
Lactate, μm/ml	2.01 ± 0.42	1.76 ± 0.21	5.15 ± 1.48†
L/P	11 ± 1	11 ± 1	39 ± 11†
MAP, torr	122 ± 7†	84 ± 4	69 ± 13
HR, beats/min	132 ± 11	159 ± 11	149 ± 11
Q̇, l/min/m ² *	4.82 ± 0.85	3.25 ± 0.59	4.45 ± 0.39
V̇ _{o₂} , ml/min/m ² *	156 ± 37	130 ± 5	82 ± 14†
Temperature, C	37.8 ± 0.3	37.5 ± 0.2	37.2 ± 0.2

* Four dogs.

† Significantly different from other values (*P* < 0.05) (paired *t* test).

TABLE 4. Control, Four-hour, and Final Values in Nine Dogs Given 1.0 mg/kg/hr Sodium Nitroprusside and 6.0 mg/kg/hr Thiosulfate (Group 3a, b) (Mean ± SE)

	Control	Four Hours	Final
Pa _{o₂} , torr	154 ± 6	146 ± 5	124 ± 9
Pa _{co₂} , torr	34 ± 1	36 ± 1	36 ± 1
pH	7.38 ± 0.01	7.38 ± 0.02	7.35 ± 0.03
BB ⁺ , mEq/l	46 ± 1	46 ± 1	44 ± 1
P _{v̄o₂} , torr*	61 ± 3	57 ± 1	48 ± 3‡
Lactate, μm/ml	2.98 ± 0.29	2.48 ± 0.33	0.80 ± 0.29†‡
L/P	14 ± 2	14 ± 1	11 ± 2‡
MAP, torr	145 ± 8†	109 ± 7	110 ± 13
HR, beats/min	179 ± 15	184 ± 13	171 ± 8
Q̇, l/min/m ² *	4.90 ± 0.35†	3.39 ± 0.40	2.89 ± 0.46
V̇ _{o₂} , ml/min/m ² *	157 ± 26	120 ± 19	128 ± 9‡
Temperature, C	37.8 ± 0.2	37.4 ± 0.1	37.4 ± 0.2

* Six dogs.

† Significantly different from other values (*P* < 0.05) (paired *t* test).

‡ Significantly different from values in untreated group (table 2) (unpaired *t* test).

hemiplegia, and stupor developed. A right carotid angiogram revealed occlusion of the middle cerebral artery, possibly embolic in origin. No neurosurgical procedure was indicated. Nitroprusside therapy was continued, and the dose required remained relatively constant for seven days. On the fifth day, serum SCN was reported to be 0.9 mg/dl (9 μg/ml). By the seventh day the patient was alert, and his neurologic status had stabilized, although a dense left hemiplegia persisted. Operation for correction of the coarctation was under consideration. During the eighth day, the dose of nitroprusside required for maintenance of blood pressure increased (fig. 8) to approximately 0.30–0.35 mg/kg/hr (5–6 μg/kg/min), and SCN had increased to 3.3 mg/dl (33 μg/ml). During this period, the patient complained of chest pain, and an ECG revealed ST segment depression; this subsequently subsided. By the tenth day, nitroprusside dose requirements again had approximately doubled (to 0.70 mg/kg/hr). Clinical concern about this dose was alleviated by the finding that serum SCN was 5 mg/dl. After approximately 14 hours at this dose, the patient was noticed to have become obtunded and tachypneic. An arterial blood-gas determination revealed severe metabolic acidosis (pH_a 7.25, base deficit 18 mEq/l, Pa_{co₂}, 19 torr). During

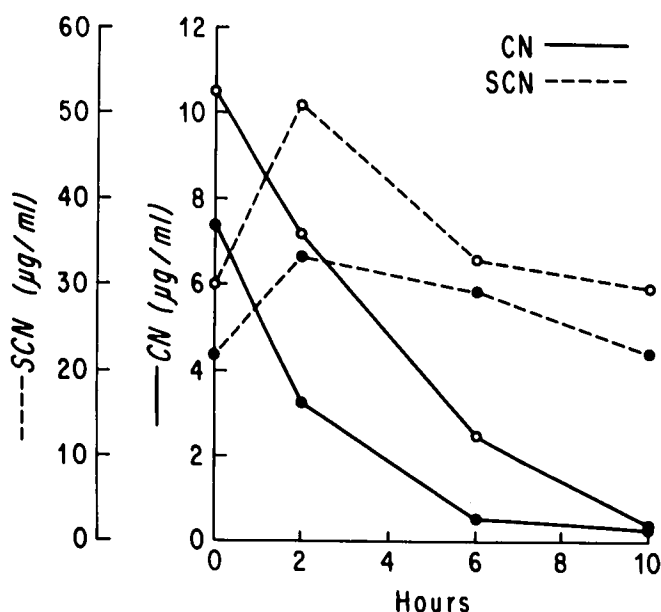


Fig. 6. Whole-blood cyanide and serum thiocyanate levels in two dogs following discontinuation of nitroprusside infusion. After ten hours, whole-blood CN levels decreased to less than 0.3 $\mu\text{g}/\text{ml}$, while serum SCN initially increased and then decreased.

this time, the nitroprusside dose had been maintained at a rate of 1 mg/kg/hr (16 $\mu\text{g}/\text{kg}/\text{min}$) for several hours. Nitroprusside was discontinued, but a progressive and rapid deterioration of the patient's status occurred, culminating in pulmonary edema, bradycardia, and cardiac arrest. Standard resuscitative measures restored cardiac function, but the EEG remained isoelectric and, after 24 hours of ventilatory support, the patient died. A whole-blood cyanide value determined 12 hours after nitroprusside had been discontinued was reported to be 0.18 $\mu\text{g}/\text{ml}$. Cyanide toxicity was considered unproven. Autopsy revealed marked stenosis of the right internal carotid and middle cerebral arteries secondary to intimal and subintimal dissecting hemorrhage, diffuse hypoxic encephalopathy with edema, and aortic coarctation.

This case raises several questions. Can nitroprusside administered in doses such as were given to this patient cause cyanide toxicity? Can simultaneous thiosulfate administration provide protection? Do serum SCN levels reflect onset of CN toxicity, as is commonly stated? Are there other routine tests that might detect early onset of toxicity? How useful is a delayed measurement of blood CN in detecting CN toxicity? The present study was designed to answer these questions.

The dog appears to be an acceptable model for the study of SNP-induced cyanide toxicity, for several reasons. The dog is relatively resistant to the hypotensive effects of nitroprusside; thus, large doses can be used without hypotension-induced artifact. In a previous study,⁵ we found that detectable cerebral metabolic cyanide toxicity developed in the dog at acutely (given in a one-hour period) administered doses exceeding 1.5 mg/kg. This is identical to the

maximum acute dose independently recommended by Vesey *et al.*⁴ based upon human blood cyanide levels following SNP infusion. Finally, the correlation between the chronic SNP dosage at which the patient reported herein showed signs of toxicity (approximately 0.7 mg/kg/hr) and the levels of SNP at which our dogs were unable to detoxify released cyanide (0.75 mg/kg/hr) provides additional evidence for the suitability of the dog model.

At 0.5 mg/kg/hr SNP, the dogs' whole-blood cyanide levels increased initially to approximately 1.0 $\mu\text{g}/\text{ml}$, but remained below 2.0 $\mu\text{g}/\text{ml}$ for 48 hours, without metabolic evidence of toxicity. At 0.75 mg/kg/hr SNP, cyanide levels increased in an approximate linear fashion, and toxicity was evident at 20–28 hours, with death at 30–38 hours. With higher doses of SNP, cyanide levels increased more rapidly, and toxicity occurred earlier. These results suggest that release of CN from SNP is dose-related and that the capability for detoxification of cyanide to thiocyanate by the rhodanase system is limited.

When thiosulfate was added to SNP, higher doses of SNP were tolerated without toxicity, indicating that a major rate-limiting factor in the rhodanase-mediated reaction is the availability of a sulfur donor (*e.g.*, thiosulfate). Evidence that increased release of CN was occurring with increased SNP dosage is obtained from the fact that thiocyanate levels were highest in the animals given thiosulfate along with otherwise toxic doses of SNP (fig. 2). Thus, SCN levels do not reflect simply rate of release of CN, but rather the capacity for detoxification of CN. This, in turn, is dependent upon availability of a sulfur donor (probably mostly thiosulfate). Accordingly, clinical measurements of SCN levels are neither indicative nor predictive of development of cyanide toxicity. The upper "safe" limit for SCN of 10 mg/dl commonly suggested^{7,8} is in fact the level above which SCN itself can be toxic.^{9,10} To our knowledge there are no data to indicate that any given SCN level will reflect or predict CN toxicity, and our results indicate the contrary. In our patient, presumed cyanide toxicity occurred at a thiocyanate level of only 5 mg/dl, and

TABLE 5. Tissue CN Levels, $\mu\text{g}/\text{g}$ (Mean \pm SE)

	Group 1 0.5 mg/kg/hr (4 Dogs)	Group 2a, b 0.75 or 1.0 mg/kg/hr (6 Dogs)	Group 3a, b 1.0 mg/kg/hr + Thiosulfate (3 Dogs)
Brain	0.65 \pm 0.37	0.50 \pm 0.21	0.55 \pm 0.21
Kidney	0.38 \pm 0.19	0.94 \pm 0.30	0.17 \pm 0.09
Liver	0.20 \pm 0.11	2.25 \pm 0.70	1.58 \pm 0.31
Heart	0.35 \pm 0.07	1.01 \pm 0.23	1.07 \pm 0.11
Muscle	0.84 \pm 0.41	1.54 \pm 0.37	0.72 \pm 0.32

in our dogs the highest thiocyanate levels were seen in animals that survived (fig. 2).

Cyanide levels in our dogs did accurately reflect development of toxicity. Metabolic evidence of toxicity appeared at 5–7 μg CN/ml. This is consistent with toxic blood levels reported in previous human case reports^{3,4,11,12} of SNP-related CN toxicity, and in other laboratory studies.^{5,13} The rapid decrease in blood CN seen after discontinuation of nitroprusside (fig. 8) emphasizes the importance of measuring CN levels during the time the nitroprusside is administered and renders interpretation of CN levels measured after discontinuing nitroprusside meaningless. Thus, in the case reported herein, the low CN levels measured 12 hours after discontinuing nitroprusside did not rule out CN toxicity.

Among commonly available laboratory tests, measurements of blood lactate (or L/P), base deficit, and mixed venous blood P_{O_2} appeared to reflect onset of CN toxicity most accurately. Metabolic acidosis is an early indicator of toxicity because progressive inactivation of cytochrome oxidase by CN results in increasing anaerobic glycolysis. Increased $P\bar{v}_{\text{O}_2}$ reflects a pathologic decrease in oxygen consumption provided cardiac output is maintained. A detectable change in the EEG pattern is probably a later sign of toxicity, as would be an alteration of the patient's sensorium. There is no apparent early hemodynamic

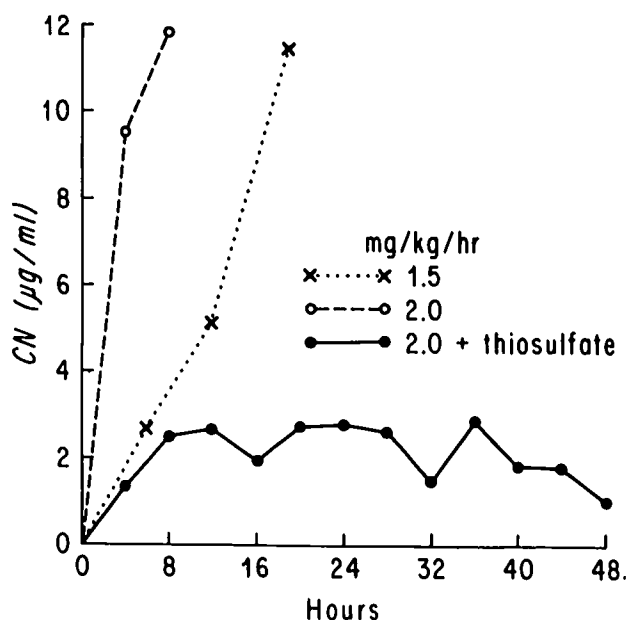


FIG. 7. Whole-blood cyanide levels in three dogs during continuous infusion of sodium nitroprusside. In dogs given either 1.5 or 2 mg/kg/hr without thiosulfate, CN increased precipitously to almost 12 $\mu\text{g}/\text{ml}$ until death occurred. In a dog given 2 $\mu\text{g}/\text{kg}/\text{hr}$ plus thiosulfate, blood CN levels were maintained at 1–3 $\mu\text{g}/\text{ml}$ for 48 hours.

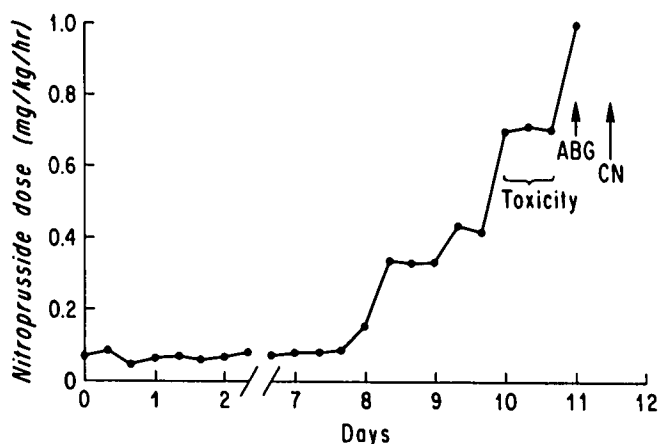


FIG. 8. The dose of sodium nitroprusside given as a continuous infusion to a 43-kg patient is charted at eight-hour intervals. Dosage was relatively constant for eight days, but thereafter progressively increased. Signs compatible with CN toxicity were apparent on the tenth day, and arterial blood gases (ABG) revealed severe metabolic acidosis at the end of that day. Nitroprusside was then discontinued. Blood CN levels were measured 12 hours later.

alteration that would signal toxicity. A current study in our laboratories has in fact revealed the myocardium to be surprisingly resistant to SNP-related CN toxicity (Tinker, unpublished observation). Detection of a decrease in whole-body O_2 consumption is also an early indicator of toxicity.

Urinary volume for 48 hours in the thiosulfate-treated dogs was approximately twice that in the untreated animals. This presumably relates to the increased rate of formation of thiocyanate and resultant diuresis. Thiosulfate-treated dogs given double maintenance fluids fared considerably better than those not given extra fluids. All four dogs given extra fluids survived 48 hours and were normal in all respects, whereas two of five thiosulfate-treated dogs not given extra fluids died late in the 48-hour period in apparent hypovolemic shock; one further animal survived 48 hours but eventually died; only two dogs in this group recovered and appeared normal. Thus, it would appear that careful attention must be given to fluid balance in the situation where thiosulfate is added to nitroprusside therapy.

The dose of thiosulfate used in this study (6 mg/kg/hr) was selected to result in a total dose every 24 hours approximately equal to that recommended for the acute treatment of existing CN toxicity (150–200 mg/kg).¹⁴ This dose had no adverse effects when given to two dogs for a 48-hour period in the absence of nitroprusside. The lack of toxicity resulting from the SCN levels produced in the thiosulfate-treated animals was also demonstrated in a single dog given thiocyanate for 48 hours (without nitroprusside).

This resulted in SCN blood levels comparable to that produced in dogs given thiosulfate plus SNP without apparent toxicity.

The results of this study, correlated with the clinical case reported herein, support the following conclusions. Sodium nitroprusside, chronically administered, results in CN toxicity at a dose of 0.75 mg/kg/hr or more. The development of CN toxicity is in large part determined by the availability of sulfur donors. Toxicity can probably be prevented or minimized by the simultaneous administration of thiosulfate. Serum SCN levels do not reflect CN levels, and are thus not useful for detecting onset of CN toxicity. Whole-blood CN levels greater than 5 $\mu\text{g/ml}$ are toxic. Measurement of blood lactate and base deficit will best permit early detection of CN toxicity; measurement of $\text{P}\bar{\text{v}}\text{O}_2$ is less commonly available and less meaningful unless cardiac output is also determined. When chronically administered, the dose of nitroprusside should not exceed 0.5 mg/kg/hr (8 $\mu\text{g/kg/min}$).

References

1. Smith RP, Kruszyna H: Nitroprusside produces cyanide poisoning via a reaction with hemoglobin. *J Pharmacol Exp Ther* 191:557-573, 1974
2. Tinker JH, Michenfelder JD: Sodium nitroprusside: Pharmacology, toxicology and therapeutics. *ANESTHESIOLOGY* 45: 294-307, 1976
3. Davies DW, Kadar D, Steward DJ, et al: A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anesthesia. *Can Anaesth Soc J* 22:547-552, 1975
4. Vesey CJ, Cole PV, Simpson PJ: Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. *Br J Anaesth* 48:651-660, 1976
5. Michenfelder JD: Cyanide release from sodium nitroprusside in the dog. *ANESTHESIOLOGY* 46:196-201, 1977
6. Ohkawa H, Ohkawa R, Yamamoto I, et al: Enzymatic mechanisms and toxicological significance of hydrogen cyanide liberation from various organothiocyanates and organonitriles in mice and houseflies. *Pest Biochem Physiol* 2:95-112, 1972
7. Greiss L, Tremblay NAG, Davies DW: The toxicity of sodium nitroprusside. *Can Anaesth Soc J* 23:480-485, 1976
8. Palmer RF, Lasseter VC: Sodium nitroprusside. *N Engl J Med* 293:294-297, 1975
9. Smith RP: Cyanate and thiocyanate: Acute toxicity. *Proc Soc Exp Biol Med* 142:1041-1044, 1973
10. Page IH, Corcoran AC, Dustan HP, et al: Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. *Circulation* 11:188-198, 1955
11. Jack RD: Toxicity of sodium nitroprusside. *Br J Anaesth* 46:952, 1974
12. Merrifield AJ, Blundell MD: Toxicity of sodium nitroprusside. *Br J Anaesth* 46:324, 1974
13. McDowall DG, Keaney NP, Turner JM, et al: The toxicity of sodium nitroprusside. *Br J Anaesth* 46:327-332, 1974
14. Swinyard EA: Noxious gases and vapors, *The Pharmacological Basis of Therapeutics*. Edited by Goodman LS, Gilman A. New York, MacMillan, 1975, pp 904-905

Obstetric Anesthesia

ROLL-OVER TEST One hundred randomly selected nulliparous, normotensive women were subjected to the roll-over test between 28 and 32 weeks' gestation. Twenty-five women had a positive test. Thirteen of those 25 women developed pre-eclampsia requiring magnesium sulfate therapy. Eight had transient hypertension during labor, requiring no therapy. Four had no evidence of hypertension during pregnancy. The false-positive rate for the 25 women with a positive roll-over test was 16 per cent. Seventy-five women had a negative roll-over test. Sixty-eight of those women had no evidence of hyper-

tension of pregnancy. Seven had evidence of transient hypertension during labor, requiring no therapy. A false-negative test was found for 10 per cent of the 75 patients with a negative roll-over test. In no case did a patient with a negative test subsequently have pre-eclampsia. The roll-over test is recommended as a routine test for every pregnant patient between 28 and 32 weeks' gestation for the early diagnosis of hypertension of pregnancy. (Marshall GW, Newman RL: Roll-over test, *Am J Obstet Gynecol* 127: 623-625, 1977.)