

Cyanide Release from Sodium Nitroprusside in the Dog

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Thirty-nine dogs (including eight from a previous study) were given during a one-hour infusion either low (<1.0 mg/kg) or high doses (>1.0 mg/kg) of sodium nitroprusside in the presence or absence of circulating methemoglobin. In animals given low doses, the metabolic effects were relatively mild and consistent with those accounted for by a reduction in arterial pressure to 40 torr. In animals given high doses (with the same arterial pressure), metabolic alterations were significantly magnified and oxygen extraction was decreased. Animals pretreated with methemoglobin and given high doses of nitroprusside (again at the same arterial pressure) showed no toxic effect of nitroprusside. In separate studies, blood and tissue levels of cyanide were measured in dogs given high doses of nitroprusside (2.5-3.5 mg/kg) in the presence or absence of methemoglobin. In dogs given methemoglobin, 60 per cent of the administered cyanide (as nitroprusside) was recovered in the blood (as cyanmethemoglobin) after a one-hour infusion. Thereafter, blood cyanide levels declined over three hours to 25 per cent of peak levels, presumably by conversion to thiocyanate, since tissue levels of cyanide were negligible. In dogs not given methemoglobin, blood cyanide levels qualitatively followed a similar pattern but quantitatively were a fourth to a third those of pretreated dogs, and tissue levels of cyanide became elevated. It is concluded that in the dog nitroprusside, acutely administered, causes cyanide toxicity at doses exceeding 1.0-1.5 mg/kg, that the release of cyanide from nitroprusside in blood is rapid and in large quantities, that detoxification (presumably by conversion of cyanide to thiocyanate) is likewise fairly rapid but insufficient to prevent toxicity, and that protection is provided by methemoglobin. (Key words: Anesthetic techniques, hypotensive; Pharmacology, nitroprusside; Pharmacology, cyanide; Brain, metabolism.)

THE POTENTIAL TOXICITY of sodium nitroprusside is now generally recognized, as is the probability that toxicity is secondary to release of cyanide from the nitroprusside molecule.¹ As yet undetermined is the toxic dose for man, whether administered acutely (as in the operating room for induced hypotension) or chronically (as in the intensive care unit for various therapeutic purposes). Estimates of the probable toxic dose have been made based upon animal studies or isolated case reports of toxicity and/or death. The most commonly stated "safe" maximal dose, acutely administered, is 3.0-3.5 mg/kg.^{1,2} Also unknown is the rate or magnitude of the release of cyanide from nitroprusside in man or animals. *In-vitro* studies suggest that eventually

all of the cyanide (five cyanide ions for each molecule of nitroprusside) is released and that the most rapid pathway for metabolic breakdown involves a nonenzymatic reaction with hemoglobin.³ Studies in guinea pigs⁴ and baboons⁵ have suggested that cyanide release is relatively slow, with its toxic effect delayed one to three hours after administration of the nitroprusside. Also unknown is the rate of detoxification of the released cyanide (via the rhodanase system) with conversion to thiocyanate. Early recognition of toxicity also poses difficulty clinically because of the absence of specific laboratory tests. Measurement of blood levels of thiocyanate has been suggested, but would probably be of little value during or following acute therapy with nitroprusside. Blood cyanide levels are not commonly obtainable, and interpretation is clouded by the lack of information concerning the relationship between blood and tissue levels of cyanide. Furthermore, when methemoglobin is present (the breakdown of one nitroprusside molecule apparently results in the obligatory formation of one methemoglobin molecule³), blood levels will be relatively high in relation to tissue levels because of the high affinity cyanide has for methemoglobin (cyanmethemoglobin). Nonspecific laboratory tests, primarily blood pH and lactate levels or lactate/pyruvate, have been suggested as the best indicators of developing cyanide toxicity.^{1,5}

In a recent study⁶ in dogs concerned with comparing various techniques for the induction of arterial hypotension, we observed apparent toxic effects of nitroprusside at doses exceeding 1.0 mg/kg, which were manifested acutely during a one-hour period of administration. In the present study, we have expanded these original observations and have included measurements of blood and tissue levels of cyanide. Additionally, we repeated these studies in dogs pretreated with methemoglobin to evaluate the protection provided and to quantitate the magnitude and rate of release of cyanide, which is captured (and thus measurable) in the form of cyanmethemoglobin.

Methods

Thirty-nine unmedicated mongrel dogs (including eight dogs from a previous study⁶) weighing 14-20 kg were studied. Anesthesia was induced with halothane (1 per cent inspired) in nitrous oxide (70 per cent) and oxygen. Succinylcholine (20 mg) was given intravenously to facilitate endotracheal intubation, and thereafter at a constant infusion rate (150 mg/hr) to maintain muscle paralysis. Catheters were inserted in a femoral artery

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for pressure measurements and blood samples, a femoral vein for blood, fluid, and drug infusions, and the pulmonary artery for blood samples. A thermistor was inserted into the right atrium for monitoring body temperature. In 20 dogs, after placement in the prone position with the head supported by a block (15 cm in height), the sagittal sinus was exposed, isolated from extracerebral communications, and cannulated as previously described for direct measurements of cerebral blood flow (CBF) and arterial-sagittal sinus blood oxygen content difference [$C_{(a-ss)O_2}$].⁷ A parietal epidural thermistor was inserted for monitoring brain temperature. Upon completion of the surgical preparation, halothane was discontinued until expired halothane (Beckman infrared analyzer) was 0.1 per cent; thereafter, inspired halothane was set at 0.1 per cent. During this period of halothane equilibration (30–45 minutes), ventilation and inspired O_2 were adjusted to provide a P_{aCO_2} of 40 ± 1 torr (mean \pm SE) and P_{aO_2} of 150 ± 4 torr. Buffer base was adjusted to 50 ± 1 mEq/l by administration of sodium bicarbonate. Brain and body temperatures were adjusted to 37.0 ± 0.1 C by heat lamps. In addition, from seven of these dogs, 10 per cent of the calculated blood volume (based upon an assumed volume of 80 ml/kg body weight) was removed, mixed with 200 mg sodium nitrite (for conversion of hemoglobin to methemoglobin), and centrifuged, and the cells were then reinfused.

After establishing these conditions, control measurements were initiated and continued for 30 minutes. CBF, $C_{(a-ss)O_2}$, and mean arterial pressure (MAP) were measured at 5-minute intervals. Blood gases and arterial concentrations of lactate and pyruvate were measured at 15-minute intervals. Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated as a product of CBF and $C_{(a-ss)O_2}$. Blood O_2 contents were calculated from measurements of oxyhemoglobin concentrations (IL CO-oximeter) and P_{O_2} . MAP was transduced by a strain gauge with the zero reference level at the mid-chest position. Lactate and pyruvate determinations were by an enzymatic method.

After control determinations, MAP was reduced to 40 torr (equivalent to a cerebral perfusion pressure of 30 torr) with an infusion of sodium nitroprusside (0.02 per cent) and maintained at this level for an hour. During this period, MAP was continuously monitored, CBF and $C_{(a-ss)O_2}$ were measured at 5-minute intervals, and blood samples for pH , P_{CO_2} , P_{O_2} , lactate, and pyruvate determinations were taken at 15-minute intervals. In about half of the animals, despite large doses of nitroprusside (as much as 3.5 mg/kg), MAP could not be maintained at 40 torr and an expiratory resistance of 5–10 cm H_2O was added. In about half of these animals, blood removal (to 200 ml) was also necessary to maintain hypotension. Because of these differences

in dose requirements, two groups of animals emerged among the 13 dogs not reinfused with methemoglobin: seven dogs required one-hour total doses of less than 1.0 mg/kg, and six dogs required doses exceeding 1.0 mg/kg. In the seven dogs given methemoglobin prior to the hypotensive period, doses of nitroprusside exceeding 1.0 mg/kg were always (deliberately) given; in about half of these, additional fluid volume (lactated Ringer's solution) was necessary to prevent a reduction in pressure to below 40 torr. By this means, three final groups of animals were created: low-dose, without methemoglobin treatment (seven dogs, four from a previous study); high-dose, without methemoglobin treatment (six dogs, four from a previous study); high-dose, with methemoglobin treatment (seven dogs).

In 17 dogs, the surgical preparation was limited to cannulation of the femoral vessels. In eight of these, 10 per cent of the calculated hemoglobin was converted to methemoglobin as previously described, and reinfused. Thereafter, all dogs were given a continuous infusion of 0.02 per cent sodium nitroprusside for an hour, resulting in a total dose of 50 mg (2.5–3.5 mg/kg). In the dogs sensitive to nitroprusside, blood pressure was maintained above 40 torr by fluid administration (lactated Ringer's solution) as necessary. Arterial blood samples were taken at 30 minutes, at the end of the infusion period (one hour), and at two hours (17 dogs); additional blood samples were taken at three and four hours from ten dogs. At the end of two hours, seven dogs were killed, and tissue samples were taken from brain, kidney, heart, and skeletal muscle. For the remaining ten dogs, tissue samples were taken at the end of four hours. All blood and tissue samples were sealed and frozen at -80 C. Subsequently, blood samples were analyzed for concentrations of cyanide and thiocyanate and tissue samples for cyanide using the method of Ohkawa *et al.*⁸ We were unable to measure tissue levels of thiocyanate because of an unexpected interference with the color reaction, which resulted in spurious high values. Based upon the blood concentrations of cyanide and thiocyanate, and the calculated blood volumes in individual dogs, the total amount of cyanide in the blood (at the time intervals sampled) was calculated and expressed as a percentage of the total amount of cyanide given in the form of nitroprusside.

From two dogs not pretreated with methemoglobin, control tissue biopsies were taken from brain, kidney, liver and skeletal muscle, followed by a one-hour infusion of 50 mg nitroprusside. Tissue biopsies were then repeated one, two, three, and four hours later. All tissue samples were analyzed for cyanide.

Results were analyzed statistically using Student's *t* test for paired data to compare initial (control)

TABLE 1. Nitroprusside Dose, Map, $P\bar{V}_{O_2}$, and Acid-Base Values in Three Groups of Dogs (Mean \pm SE)

	Low-dose Untreated		High-dose Untreated		High-dose Treated	
	Initial	Final	Initial	Final	Initial	Final
Nitroprusside, mg/kg	—	0.5 \pm 0.1	—	2.1 \pm 0.4	—	1.9 \pm 0.3
MAP, torr	118 \pm 7	42 \pm 1	137 \pm 4	42 \pm 4	132 \pm 6	43 \pm 2
$P\bar{V}_{O_2}$, torr	53 \pm 2	37 \pm 3	56 \pm 1	53†* \pm 4	50 \pm 2	34 \pm 2
pH	7.40 \pm 0.01	7.31 \pm 0.02	7.39 \pm 0.01	7.18* \pm 0.02	7.43 \pm 0.01	7.30 \pm 0.02
Buffer base, mEq/l	49 \pm 1	43 \pm 1	49 \pm 1	36* \pm 1	51 \pm 1	44 \pm 1
Lactate, μ m/ml	3.49 \pm 0.24	4.42† \pm 0.49	3.54 \pm 0.35	9.68* \pm 1.62	3.76 \pm 0.34	5.29 \pm 0.48
Lactate/pyruvate	15 \pm 1	22 \pm 3	15 \pm 1	64* \pm 12	12 \pm 0	17 \pm 2

* Significantly different from final values in the low-dose untreated and high-dose treated groups, $P < 0.05$.

† Final values not significantly different from initial values; all other final values differ significantly from initial values, $P < 0.05$.

TABLE 2. Cerebral Hemodynamic and Metabolic Values in Three Groups of Dogs

	Low-dose Untreated (n = 7)		High-dose Untreated (n = 6)		High-dose Treated (n = 7)	
	Initial	Final	Initial	Final	Initial	Final
CBF, ml/100 g/min	95 \pm 21	48 \pm 7	91 \pm 9	46 \pm 4	110 \pm 11	47 \pm 4
P_{SSO_2} torr	56 \pm 3	35 \pm 2	56 \pm 3	50†* \pm 4	56 \pm 3	29 \pm 2
CMR_{O_2} , ml/100 g/min	5.23 \pm 0.36	4.80† \pm 0.47	4.97 \pm 0.30	3.75* \pm 0.31	5.56 \pm 0.33	5.06† \pm 0.27
Lactate, μ m/gm	(2.06† \pm 0.20)	3.05 \pm 0.41	—	10.60* \pm 1.71	—	5.40 \pm 0.89
Lactate/pyruvate	(15† \pm 2)	20† \pm 4	—	46* \pm 8	—	22 \pm 2
ATP, μ m/g	(2.24† \pm 0.03)	1.82 \pm 0.06	—	1.73 \pm 0.10	—	1.85 \pm 0.04
Phosphocreatine, μ m/g	(4.96† \pm 0.41)	2.27 \pm 0.19	—	1.23* \pm 0.18	—	2.22 \pm 0.15

* Final values significantly different from final values in low-dose untreated and high-dose treated groups, $P < 0.05$.

† Not significantly different from initial values; all other final values differ significantly from initial values or previously reported control values (for brain lactate, lactate/pyruvate, ATP, and PCr), $P < 0.05$.

‡ Previously reported control values.^{13,14}

and final values in the same dogs and Student's *t* test for unpaired data to compare final values in the high-dose and low-dose animals. A probability of less than 5 per cent that differences were due to chance was considered significant.

Results

The systemic and cerebral effects of one hour of hypotension at 40 torr in this preparation were reported previously, and are exemplified by the results in the dogs given low doses of nitroprusside (<1.0 mg/kg) (tables 1 and 2). Significant systemic effects include reductions in mixed venous oxygen tension ($P\bar{V}_{O_2}$), pH, and buffer base, and increases in blood lactate and lactate/pyruvate. Significant cerebral effects include reductions in CBF, sagittal sinus oxygen tension (P_{SSO_2}), brain ATP, and phosphocreatine, and an increase in brain

lactate. In dogs given high doses of nitroprusside (>1.0 mg/kg) and not pretreated with methemoglobin, all of the metabolic derangements were significantly magnified, and reductions in $P\bar{V}_{O_2}$ and P_{SSO_2} were not observed. These observations in a total of only eight dogs were described previously and they were expanded in the present study to include 13 dogs. Comparing the one-hour total dose of nitroprusside given with the resulting brain lactate levels in these 13 dogs. (fig. 1) suggests a linear relationship. A similar relationship of nitroprusside dose to the reduction in CMR_{O_2} was also apparent.

In the dogs pretreated with methemoglobin and then given large doses of nitroprusside, there was no apparent toxicity due to the nitroprusside, and the results were those expected secondary to a reduction in MAP to 40 torr only. Compared with the high-dose animals not given methemoglobin, the metabolic derangements were all signif-

icantly less and not different from those seen in the low-dose animals. Similarly, the expected reductions in $P\bar{V}O_2$ and P_{SSO_2} were observed and were of magnitudes similar to those seen in the low-dose animals.

Comparing blood levels of cyanide in animals given methemoglobin with those in dogs not so treated, significant differences are again apparent (fig. 2). At the end of a one-hour infusion of 50 mg nitroprusside, blood levels in treated dogs were three times those seen in untreated dogs, and were equivalent to approximately 60 per cent of the total cyanide given in the form of nitroprusside. With cessation of the infusion, blood cyanide levels decreased progressively in both groups, but they remained elevated even after four hours. Blood thiocyanate levels were similar in the two groups and tended to increase slightly with time (fig. 3). Differences in tissue levels of cyanide between the treated and untreated animals were also observed. The highest levels were found in the skeletal muscle of untreated animals, whereas in the treated animals, only very low concentrations were found (in only three of seven animals). Similarly, in the treated dogs, no cyanide was recovered in brain or liver, whereas cyanide was inconsistently found in these tissues in untreated animals (four of nine). Cyanide was inconsistently recovered in both groups of animals from the myocardium and kidney, but higher levels were again found (and with greater frequency) in the untreated animals. The inconsistency in the recoveries of cyanide from the various tissues was not accounted for by the different times of biopsy (after either two or four hours), since the distributions of cyanide-free tissues were similar in the two groups, and in the cyanide-

Relationship Of Brain Lactate To Dose Of Nitroprusside

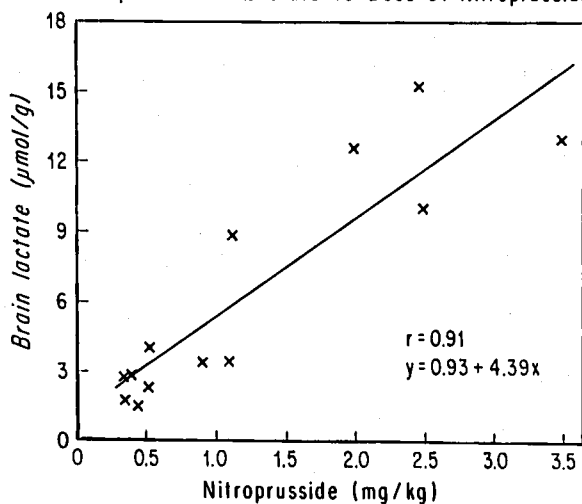


FIG. 1. The relationship of brain lactate concentration to total dose of sodium nitroprusside administered. At doses exceeding 1.0 mg/kg, a progressive elevation in brain lactate occurs and a linear relationship is suggested.

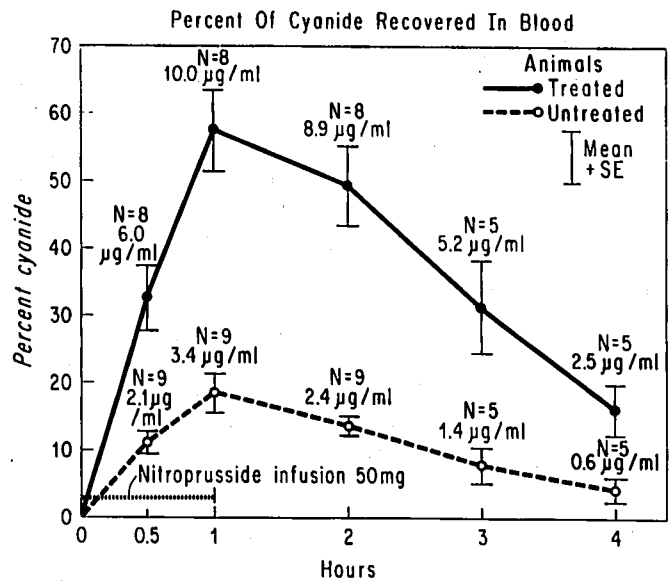


FIG. 2. Percentages of administered cyanide (as nitroprusside) recovered in the blood of dogs with and without methemoglobin pretreatment. At each point, the number of dogs and the mean blood cyanide concentration are indicated. In animals given methemoglobin, 60 per cent of the administered cyanide is recoverable at the end of the one-hour infusion as cyanmethemoglobin. Blood levels then decline, presumably by conversion to thiocyanate in the tissues. Animals not pretreated had blood levels a fourth to a third those seen in the treated animals, presumably because of binding of cyanide to cytochrome oxidase in the tissues.

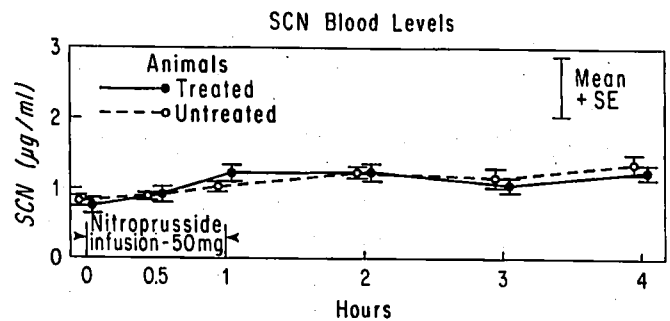


FIG. 3. Blood thiocyanate levels in dogs with and without methemoglobin pretreatment. Blood levels were low and were similar in the two groups, but tended to increase slightly with time.

containing tissue, the concentrations were not meaningfully different at the two different time intervals.

In the two dogs from which repeat tissue biopsies were taken following 50 mg nitroprusside (in the absence of methemoglobin), the variability between dogs and among individual organs is apparent (fig. 4). In one of these dogs, tissue levels were relatively high and tended to peak at 1-2 hours, whereas in the other dog, tissue levels were low and tended to peak relatively late.

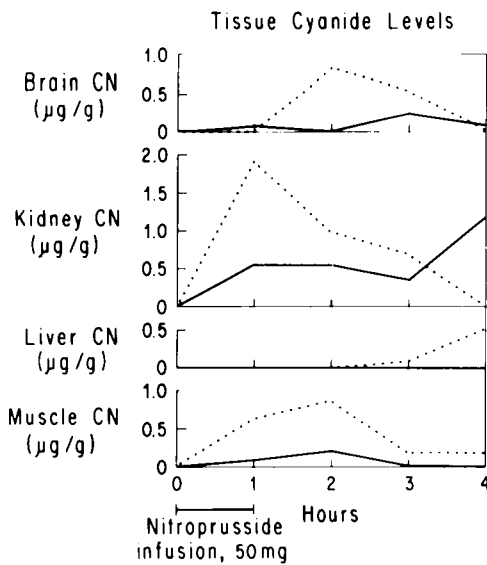


FIG. 4. Tissue cyanide levels in two untreated dogs following 50 mg nitroprusside. The variability between dogs and among different organs in tissue cyanide levels (in the absence of methemoglobin) is apparent.

Discussion

These results demonstrate that the potential toxic effects of nitroprusside are due to the release of cyanide. In dogs, significant systemic and cerebral metabolic derangements are demonstrable following acutely administered doses exceeding 1.0–1.5 mg/kg. The combination of tissue hypoxia with normal or elevated venous O_2 levels is the hallmark of cytotoxic hypoxia as produced by cyanide. The rapid metabolic degradation of nitroprusside with release of cyanide was apparent in our methemoglobin-treated dogs, such that 60 per cent of the cyanide administered as nitroprusside was recovered in the blood (in the form of cyanmethemoglobin) immediately following a one-hour infusion of 50 mg nitroprusside. That methemoglobin protected the dog was apparent both in the metabolic studies and in the low or absent cyanide concentrations found in the various tissues examined. In the absence of methemoglobin, blood cyanide levels were a third those observed with methemoglobin, and this is presumably explained by the

rapid exodus of cyanide into the tissues to combine with cytochrome oxidase. Again, both the metabolic studies and the tissue level of cyanide support this conclusion.

The affinity of cyanide for methemoglobin is well known, and is the basis for the treatment of cyanide poisoning.⁹ Therapeutically, sodium nitrite is administered in a dose sufficient to produce high levels of methemoglobin, which then competes with the cytochrome oxidase for the cyanide ion. Since the concentration gradient favors methemoglobin, cyanmethemoglobin is formed and cytochrome oxidase is restored. The final step in detoxification requires the rhodanase system, which catalyzes a reaction between thiosulfate and cyanide to form thiocyanate; the latter is then excreted in the urine. Thus, prophylactic treatment with methemoglobin (as in our dogs) would be expected to result in capture of the bulk of the cyanide released from conversion of the cyanide to thiocyanate. In our animals so treated, the progressive decreases in blood cyanide levels following the nitroprusside infusion (without meaningful increases in either tissue cyanide levels or blood thiocyanate levels) indicate fairly rapid detoxification, presumably by conversion of cyanide to thiocyanate in the tissues (which we were unable to quantitate). The inconsistent recovery of cyanide in the tissues of our untreated animals might also be explained by conversion to thiocyanate with considerable variability among individual animals. The limiting step in this conversion process is said to be the availability of endogenous thiosulfate.⁹ We assume, therefore, that variability in the recovery of cyanide from various tissues may be accounted for by variability in the availability of thiosulfate.

Direct clinical application of the results of this study is problematical, other than to state the obvious: nitroprusside can cause cyanide toxicity. In the dog, toxicity is demonstrable at doses exceeding 1.0–1.5 mg/kg (acutely administered). In the baboon, McDowall *et al.*⁵ recognized toxicity at doses exceeding 4.0 mg/kg (acutely administered), whereas no toxicity was observed at doses below 1.6 mg/kg/hr. Clinical experience clearly indicates that acutely administered doses of less than 1.0–1.5 mg/kg are well tolerated, whereas toxicity and death in man have been reported to occur at doses exceeding 3.0 mg/kg² and 7.0 mg/kg,¹⁰ respectively. Species variability may in part be accounted for by differences in the rates of release of cyanide from nitroprusside.³ In our dogs, the rate of increase in blood cyanide paralleled the accumulated dose given, and the blood cyanide level immediately began to decline with cessation of the infusion. This suggests a relatively rapid release of cyanide. However, in guinea pigs⁴ and baboons,⁵ there appears to be a delay in the onset of toxicity of as much as one to three hours. Again, there is no

TABLE 3. Tissue Cyanide Levels in Treated and Untreated Dogs, $\mu\text{g/g}$ (Wet Weight), Mean \pm SE

	Treated	Untreated
Skeletal muscle	0.08 \dagger \pm 0.04 (4/7)*	1.07 \pm 0.40 (2/9)
Liver	0 (8/8)	0.28 \pm 0.13 (5/9)
Brain	0 (8/8)	0.17 \pm 0.09 (5/9)
Myocardium	0.17 \pm 0.07 (3/6)	0.54 \pm 0.17 (2/9)
Kidney	0.08 \pm 0.05 (6/8)	0.17 \pm 0.09 (5/9)

* Paranthetical numbers indicate frequencies of zero cyanide levels.

\dagger Significantly different from untreated, $P < 0.05$.

information obtained in man (*in vivo*) concerning the rate of cyanide release from nitroprusside.

It is also apparent from this study that measurement of blood levels of cyanide or thiocyanate will not reflect the magnitude of cyanide released (in the absence of methemoglobin). Acute changes in blood thiocyanate do not occur, and at least two thirds of the cyanide released is apparently rapidly bound in the tissues. Lethal blood levels in man have been reported to be as low as 0.34 mg/100 ml (3.4 μ g/ml),¹¹ but this, too, must vary with the rate and total dose of cyanide administered (or in the case of nitroprusside, with the rate of cyanide release as well as total dose). The most sensitive metabolic indicators of cyanide toxicity appear to be blood pH, blood lactate (or lactate/pyruvate), $P\bar{v}_{O_2}$, CMR_{O_2} , Pss_{O_2} , and brain lactate (or lactate/pyruvate). Of these, blood pH, lactate, and $P\bar{v}_{O_2}$ are easily obtainable clinically and should be measured when cyanide toxicity is suspected.

Prophylaxis and/or treatment of cyanide toxicity in anticipation of or following administration of nitroprusside is also a controversial clinical problem. The efficacy of methemoglobin is obvious, but it is of itself potentially hazardous. Thus, the administration of sodium nitrite should probably be considered for treatment only, and then only in the face of imminent disaster. Hydroxocobalamin (vitamin B_{12a}) has been suggested as being useful for both prophylaxis and treatment, and has been demonstrated to be effective experimentally,¹² presumably by binding cyanide to form cyanocobalamin (vitamin B₁₂). Experience in man is, however, very limited; proper dosage and possible toxic effects have not been established. Since the availability of thiosulfate is considered to be an important rate-limiting factor in the conversion of cyanide to thiocyanate, it has been used to treat cyanide toxicity and would presumably be useful prophylactically as well. Clearly, anyone using sodium nitroprusside for clinical purposes should be aware of the various measures available for the prevention and treatment of cyanide toxicity. However, the most important consideration must be simply to avoid administering doses sufficient to cause toxicity. Until additional information is available in man, it would seem prudent to limit sodium nitroprusside (acutely administered) to a maximum total dose of 1.0–1.5 mg/kg.

ADDENDUM

Recently, Vesey *et al.*¹⁵ reported human studies of blood cyanide and thiocyanate concentrations following

nitroprusside administration and concluded that the dose of nitroprusside should not exceed 1.5 mg/kg during short-term infusions.

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