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Laboratory Report

Nitroprusside-induced Cyanide Poisoning:

Antidotal Effect of Hydroxocobalamin

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Sodium nitroprusside was investigated as a potential source of cyanide poisoning. Whole-blood cyanide determinations were performed on arterial samples from baboons receiving nitroprusside while anesthetized. There was a statistically significant increase in cyanide levels, as well as development of tachyphylaxis and severe metabolic acidosis. Hydroxocobalamin (vitamin B_{12a}) infused simultaneously with nitroprusside significantly lessened the increase in cyanide levels and eliminated the development of metabolic acidosis. Nitroprusside can cause cyanide intoxication in the baboon, and hydroxocobalamin appears to be an effective antidote. (Key words: Toxicity, cyanide; Biotransformation, nitroprusside; Anesthetic techniques, hypotension, induced, nitroprusside; Pharmacology, hydroxocobalamin.)

SODIUM NITROPRUSSIDE ($Na_2Fe(CN)_5NO \cdot 2H_2O$) has become increasingly useful in the treatment of hypertensive crises,[1,2] acute myocardial infarction,[3] congestive heart failure,[4] severe mitral regurgitation,[5,6] and the production of elective hypotension during anesthesia.[7-9] Recently, however, several deaths of patients receiving this drug have been reported[10-12]; all of these deaths were compatible with the clinical picture of cyanide poisoning.

In order to investigate the significance of cyanide in nitroprusside biodegradation, we have infused nitroprusside into baboons while measuring whole-blood cyanide levels, as well as assessing the metabolic acid–base status of the animals. We have further investigated the usefulness of vitamin B_{12a} (hydroxocobalamin) as an antidote to cyanide in this subhuman primate.

Materials and Methods

Anesthesia was induced in healthy baboons, weighing 20 to 30 kg, with approximately 5 mg/kg ketamine, given intramuscularly. Endotracheal intubation was accomplished and anesthesia was maintained with 0.5 per cent halothane and 60 per cent nitrous oxide in oxygen via a semiclosed circle absorption system. The animals were mechanically ventilated to maintain Pa_{CO_2} between 35 and 45 torr. Blood pressure was monitored via a femoral-artery cannula connected to a Sanborn 267AC pressure transducer, utilizing a Sanborn 350–1100C preamplifier and an H-P 7700 recorder. Nasopharyngeal temperature was monitored with a Yellow Springs telethermometer, and a warming blanket was used to maintain normothermia. All experiments were done with the animals supine. Arterial blood samples (5 ml) were obtained at 15-minute intervals during a control period until duplicate Pa_{CO_2} values were in the desired range; following this, a sample of arterial blood was drawn for a baseline cyanide level, nitroprusside infusion begun, and arterial blood sampled every 30 minutes for determinations of Pa_{O_2}, Pa_{CO_2}, *p*H, and blood cyanide. Cyanide determinations were done by the method of Boxer and Rickards[13] as applied to biological

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fluids by Feldstein and Klendshoj.[11] This method does not measure cyanide present as vitamin B_{12} (cyanocobalamin).

Base excess values were determined using an Instrumentation Laboratories *p*H–Blood Gas Calculator. In all animals an attempt was made to infuse sodium nitroprusside intravenously at a rate sufficient to maintain a mean arterial blood pressure of 40 torr; the infusion was continued for as long as two hours or until 500 mg had been administered. Anesthesia was maintained and the baboons observed for a total of four hours, at the end of which time they were allowed to recover.

In the first experimental group (baboons 1–4) sodium nitroprusside alone was infused. In the second experimental group (baboons 5–9) the infusate was a combination of sodium nitroprusside and vitamin B_{12a} such that 5 moles of B_{12a} were present for each mole of nitroprusside (22.5 mg B_{12a} per 1 mg nitroprusside). This ratio was selected since each molecule of nitroprusside contains five cyanide groups, and since we wished to provide at least one B_{12a} molecule for each cyanide group that could theoretically be released.

TABLE 1. Rates of Nitroprusside Infusion (μg/kg/min)

	Nitroprusside Alone				Nitroprusside + B_{12a}				
	Baboon 1	Baboon 2	Baboon 3	Baboon 4	Baboon 5	Baboon 6	Baboon 7	Baboon 8	Baboon 9
$T_{minutes}$									
T_0–T_{30}	14.5	22.2	19.6	35.5	75.5	103.6	496.9	219.7	757.6
T_{30}–T_{60}	40.5	72.2	215.7	100.5	463.9	374.8	401.4	586.1	*
T_{60}–T_{90}	110.3	400.0	305.9	455.1	*	956.9‡	*	*	*
T_{90}–T_{120}	287.4	666.7†	*	*	*	*	*	*	*

* Total dose infused prior to this period.
† T_{90}–T_{95}.
‡ T_{60}–T_{70}.

TABLE 2. Whole-Blood Cyanide (μg/100 ml)

	Nitroprusside Alone				Nitroprusside + B_{12a}				
	Baboon 1	Baboon 2	Baboon 3	Baboon 4	Baboon 5	Baboon 6	Baboon 7	Baboon 8	Baboon 9
$T_{minutes}$									
T_0	52	0.94	0	3.6	3.6	0.39	0	1.5	2.3
T_{60}	108	359	359	312	129	256	177	212	255
T_{120}	520	801	728	653	357	346	432	445	642
T_{180}	686	1253	1102	998	434	575	679	627	803
T_{240}	845	1773	1435	1272	291	536	606	416	567

TABLE 3. Base Excess (mEq/l)

	Nitroprusside Alone				Nitroprusside + B_{12a}				
	Baboon 1	Baboon 2	Baboon 3	Baboon 4	Baboon 5	Baboon 6	Baboon 7	Baboon 8	Baboon 9
$T_{minutes}$									
T_0	4	6	12	3	5	10	13	9	9
T_{60}	5	3	4	−1	7	10	10	8	9
T_{120}	−2	−8	−3	−5	9	9	8	7	—
T_{180}	−4	−15	−10	−7	11	10	10	7	10
T_{240}	−10	−25	−17	−11	11	9	9	8	12

Analysis of the data was by the rank-sum method.

Results

Group I

In all four animals we found it impossible to maintain the mean arterial blood pressure at 40 torr for more than 30 minutes. While there was no problem in achieving this degree of hypotension initially, the mean pressure quickly rose despite an ever-increasing rate of nitroprusside infusion (table 1). A maximum of 500 mg of nitroprusside was used in all cases, with a single exception receiving 545 mg. There was a progressive increase in whole blood cyanide levels (table 2) during the entire four-hour experimental period; the increase was significant ($P \leq 0.005$) at the end of the experiment as compared with the baseline value. There was also a significant change ($P \leq 0.025$) in acid–base status from baseline to the end of the observation period, with the development of profound metabolic acidoses (table 3). Within 30 minutes of discontinuing the nitroprusside infusion, every baboon became hypotensive, with mean arterial pressures between 25 and 35 torr. One of the four animals developed ventricular fibrillation at the end of the experimental period, while the other three failed to resume spontaneous respirations after discontinuation of the anesthesia; all the animals in this group died within 30 minutes.

Group II

There was no statistically significant difference ($P > 0.05$) between weights or control values for either cyanide levels or base excess values in Group I and Group II. The baboons in Group II were treated in the same manner as those in the first experiment except that vitamin B_{12a} was added to the nitroprusside solution. Again, it was impossible to maintain the blood pressure at a mean of 40 torr for more than 30 minutes in any animal despite increasing the rate of the nitroprusside–B_{12a} infusion. These animals also showed a significant increase ($P \leq 0.005$) in blood cyanide levels 30 minutes after the start of the infusion, compared with baseline values; however, by 90 minutes the increase was significantly less ($P \leq 0.025$) compared with levels in the animals receiving nitroprusside alone (fig. 1). Several important differences found were that the baboons of Group II: 1) did not develop metabolic acidosis, 2) all promptly resumed spontaneous respirations, and 3) all survived the experiment.

Discussion

Each sodium nitroprusside molecule contains five equivalents of cyanide. Smith and Kruszyna[15] have demonstrated that the reaction of nitroprusside with hemoglobin leads to the release of cyanide. These authors suggest that in the reaction between hemoglobin and a nitroprusside molecule five cyanides and one methemoglobin molecule are formed; if this were the case, then the methemoglobin thus formed would be able to detoxify a single cyanide by the formation of cyanmethemoglobin. Thus, the biotransformation of a nitroprusside molecule would result in the release of four free cyanide ions. This thesis is supported by their experiments showing that, when administered intraperitoneally to mice, the molar LD_{50} for nitroprusside is about a fourth that of sodium cyanide.

Several deaths of anesthetized patients who received sodium nitroprusside for the production of elective hypotension have recently been reported.[10–12] Without exception, the clinical courses of these patients were characterized by the development of tachyphylaxis and profound metabolic acidoses. In one case[12] a high blood cyanide level was found at autopsy. It must be noted, however, that these patients received very large doses of nitroprusside; a 14-year-old boy received 400 mg over an 80-minute period, while two adult patients each received 750 mg during the course of anesthesia.

McDowall *et al.*,[16] using a protocol similar to ours, found that they had no difficulty inducing hypotension to a mean arterial pressure of 40 torr for two hours in four of their eight baboons. Although these animals developed mild metabolic acidoses, they all recovered their normal blood pressures after discontinuation of the nitroprusside. The remaining four baboons, however, reacted quite differently

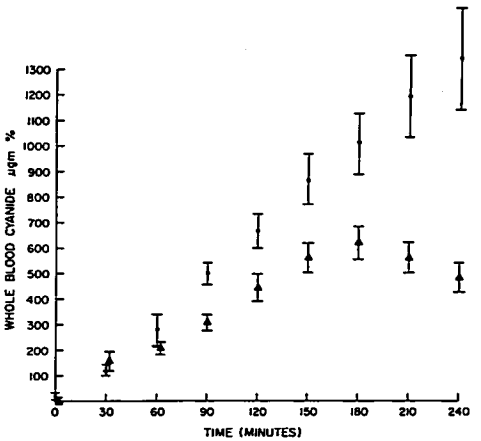

FIG. 1. Mean ± SEM values for whole blood cyanide levels (µg/100 ml) in nitroprusside-alone-treated baboons (·) and nitroprusside–B_{12a}-treated baboons (▲).

to the nitroprusside infusion; they each developed tachyphylaxis, significant metabolic acidosis, and finally, circulatory collapse. While cyanide levels were not determined in this study, the authors suggest that cyanide release was the cause of the nitroprusside toxicity.

Vesey *et al.*[17] measured plasma cyanide levels in patients receiving nitroprusside infusions. They reported a statistically significant increase in plasma cyanide after the infusion, but none of the levels appeared to be clinically important. They point out that most of the cyanide in blood is in the erythrocyte; indeed, in one patient in whose case they determined both plasma and erythrocyte cyanide levels, the plasma:erythrocyte cyanide ratio was almost 1:100. The clinical course of their patient is not described, other than that he was 46 years old and had received 2,277 mg nitroprusside over five days. His highest reported blood cyanide level was 836 µg/100 ml, which is in the range of lethal reported blood cyanide levels.[18] When this patient received 5 mg vitamin B_{12a} intravenously there was essentially no change in the plasma cyanide level, but the erythrocyte cyanide level decreased from 32 to 15.7 µmoles/100 ml.

The administration of vitamin B_{12a} has been suggested by several authors[19–21] as therapy for cyanide intoxication. Kaczka *et al.*[22] have demonstrated that *in vitro* the reaction of vitamin B_{12a} with cyanide results in the replacement of a hydroxyl group by a cyano group, with the subsequent formation of cyanocobalamin (vitamin B_{12}). We previously demonstrated the efficacy of vitamin B_{12a} as an antidote to acute cyanide intoxication in guinea pigs.[23] The present data confirm these earlier investigations, since all four baboons receiving nitroprusside alone did not survive the experiment, while all five animals receiving nitroprusside and vitamin B_{12a} recovered from the experiment.

Lutier[20] reported using 5-g doses of vitamin B_{12a} intravenously in three adult patients who had cyanide intoxication. These patients also received cobalt EDTA and other general supportive measures; all three were successfully resuscitated. We know of no case in which large doses of B_{12a} have been used as the sole therapy for human cyanide intoxication.

Vitamin B_{12a} is water-soluble, and large amounts are apparently rapidly excreted in the urine. In our experiments, within 30 minutes of administration of vitamin B_{12a}, the baboons'

urine turned dark purple; also, the animals' skin and mucous membranes became deep fuchsia, an effect that was gone within several days.

We postulate that the development of tachyphylaxis to nitroprusside is due to the accumulation of cyanide in the blood. Since cyanide produces its lethal effect by blocking the utilization of oxygen at the level of the cytochrome oxidase system, the signs and symptoms are those of acute tissue hypoxia. It would therefore be reasonable to expect that hypertension and tachycardia would initially occur under these circumstances, and that this response is able to overwhelm the vascular smooth muscle relaxation produced by the nitroprusside molecule. Another hypothesis is that the cyanide poisons the vascular smooth muscle, preventing its relaxation.

In either case it is likely that once a minimum (but as yet unknown) cyanide level is reached, the continued infusion of nitroprusside will not produce hypotension until cardiovascular collapse supervenes. That the baboons in both experimental groups developed tachyphylaxis may be an indication that this minimum cyanide level was reached in each animal.

There are still no reliable data regarding the maximum dose of nitroprusside that can be administered safely. Davies *et al.*[12] have recommended 3.5 mg/kg as an upper limit. They base this on their theoretical grounds that this dose of nitroprusside is equivalent to 1.5 mg/kg cyanide, and that 3.0 mg/kg cyanide is a lethal dose. This concept, however, does not allow for variability in the rate of infusion, since the total amount safely infused may be greater when given over a prolonged period.

Until more experimental data become available, we recommend that, in the operating room, sodium nitroprusside be administered at a rate no faster than 10 μg/kg/min, for a maximum of 300 minutes at this rate. Resistance to the drug, or development of tachyphylaxis, should be cause for its immediate discontinuation. Arterial blood gases should be frequently monitored and the development of an otherwise unexplained metabolic acidosis should also be cause for immediate termination of nitroprusside infusion. Further deterioration of the patient's condition should arouse the strong suspicion of cyanide intoxication, and appropriate therapy should be instituted.

Currently, approved treatment of cyanide intoxication consists of the administration of amyl nitrite and sodium nitrite in order to form methemoglobin.[24,25] Cyanide will combine with the Fe^{+++} of methemoglobin, competitively removing the cyanide from cytochrome oxidase, permitting cellular respiration to continue. Thiosulfate is then administered to facilitate detoxification of cyanide to thiocyanate. While this method is effective, it does have the disadvantage of producing non-oxygen-carrying methemoglobin. We know of at least one death produced by overzealous administration of nitrite to a patient who had ingested a sublethal amount of cyanide.[26] While there are only limited data presently available, it appears that vitamin B_{12a} may offer an effective alternative to nitrite therapy, with the important advantage of a greater margin of safety.

There can be no doubt that cyanide poisoning may occur during the administration of sodium nitroprusside. Tachyphylaxis and the development of a metabolic acidosis are important signs of cyanide accumulation. In the future, hydroxocobalamin (vitamin B_{12a}) may prove to be an effective and nontoxic antidote to cyanide intoxication.

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